An Investigation of the Semantic Memory and Executive Function Deficits in Schizophrenia

Submitted by

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Notice 1

Notice 2

ACKNOWLEDGEMENTS

Firstly, I would like to thank my family for providing me with so much support throughout my thesis. I would also like to sincerely thank Professor Susan L. Rossell for being a wonderful supervisor, employer and friend. I would like to thank my friends who were willing to read manuscript drafts and participate in my research. In particular, I would like to thank Belinda Smith for finding me so many willing participants. A big thank you must also go out to Eric Tan and Tamsyn Van Rheenen for providing the support and understanding that can only come from fellow PhD students. Last but not least, I would like to thank all the schizophrenia participants who kindly gave their time in the name of research.

Addendum

- P43, line 4 delete "What is not contentious is the finding that deficits in EF significantly predict long term functioning (Reed, Harrow, Herbener, & Martin, 2002) and as such, further examination of EF deficits is required. As a result of its effect on outcome, EF is often a key element in contemporary neurocognitive models of psychosis."
- P43, line 4 "Research suggests that deficits in EF predict long term outcome (Reed, Harrow, Herbener, & Martin, 2002) reinforcing the need for furthering our understanding of EF deficits. EF is often a key element in contemporary neurocognitive models of psychosis."
- P47, starting line 10 change "Two such batteries include the Hodges Semantic Memory Test Battery (Hodges, Salmon, & Butters, 1992) and Pyramids and Palm Trees (Howard & Patterson, 1992)" to "Two such instruments include the Hodges Semantic Memory Test Battery (Hodges et al., 1992) and Pyramids and Palm Trees test (Howard & Patterson, 1992)."
- P65, line 14 delete the following: "It is suggested that a difficulty in accessing verbal memory generally should affect responses to the phonological and semantic fluency task equally"
- P66, line 10 insert the following: "Further, given that the authors have relied on only one criterion to determine whether deficits reflect and access or storage problem, the results must be interpreted with caution."
- P128, line 16 Change "and general intellectual decline" to "intellectual decline in the transition to illness"
- P 168, line 19 delete "After some consideration, it was decided that masking the implicit priming task would be inappropriate because (1) there is only a small body of schizophrenia examining masked indirect priming (Del Cul A, 2006; Kiefer, Martens, Weisbrod, Hermle, & Spitzer, 2009; Quelen, Grainger, & Raymondet, 2005a; Wentura, Moritz, & Frings, 2008) and (2) there is only the one analogue study for comparison (Angwin et al., 2004). Instead, a short SOA was used as there is a wealth of data for comparison purposes, including a review (S. L. Rossell & Stefanovic, 2007) and meta-analysis (Pomarol-Clotet, Oh, Laws, & McKenna, 2008). Some might still argue that a semantic priming task with a short SOA and a distractor task might not meet the most stringent criteria for an 'implicit task' as there is still the possibility that participants might notice that some pairs are related. The differences between the implicit and explicit…"
- P 168, line 19 insert "After some consideration, it was decided that masking the implicit priming task would be inappropriate because there is only a small body of schizophrenia examining masked indirect priming (Del Cul A, 2006; Kiefer, Martens, Weisbrod, Hermle, & Spitzer, 2009; Quelen, Grainger, & Raymondet,

2005a; Wentura, Moritz, & Frings, 2008). The differences between the implicit and explicit…"

- P169, line 13 insert the following: "Some participants had experimented with illicit substances but those with a history of regular drug use were excluded."
- P182, line 18 delete the following: "Effect sizes in this study were smaller than those previously reported using ketamine administration (Morgan, Rossell, et al., 2006; Stefanovic et al., 2009). One potential reason for this is that this study used more semantic tasks in the session than other studies have. Increased awareness of semantic pairs can change the strategies that people use across the session. Given that the tasks were counterbalanced then this would have affected all the tasks equally, but also resulted in less clear priming across all the measures."
- P183 line 3 "Given the symptoms experienced, some anxiety may have been present for participants under ketamine that was not present during placebo. Anxiety can slow semantic processing (Hartley et al 1982) but when the speed across conditions was compared, there was no slowing associated with the ketamine condition.

Hartley, L. R., Spencer, J., & Williamson, J. (1982). Anxiety, diazepam and retrieval from semantic memory. *Psychopharmacology, 76*(3), 291-293. doi: 10.1007/bf00432564

- P192, line 12 delete "the Pyramids and Palm Trees Battery (an explicit semantic battery)"
- P192, line 12 insert "the Pyramids and Palm Trees test (a test of explicit semantic memory)"
- P194, line 21 delete "The participants were recruited via advertisements at Monash University."
- P194, line 21 insert "Adverts were displayed at Monash University and additional participants were recruited from the Alfred Hospital where researchers were based."
- P216 line 9 delete "Diagnosis and symptom profile was investigated using the Structured Clinical Interview Diagnostic (SCID) (First, Spitzer, Gibbon, & Williams, 1997)"
- P216 line 9 insert "All participants identifying themselves as having psychosis met DSM IV criteria for schizophrenia. The Structured Clinical Interview Diagnostic (SCID) (First, Spitzer, Gibbon, & Williams, 1997) was used to confirm diagnosis."
- P221, line 16 insert "Controlling for age did not alter the findings significantly."
- P221 insert the following table:

Table 1. Demographic Information

	Schizophrenia (N=18)	Controls (N=21)
Male/Female	8/10	6/15
Age (years)*	40 (12.2)	30 (9.8)
Education (years)	14.5 (4.0)	15.7 (2.1)
WTAR IQ	102 (13.27)	102 (7.9)
TLC (total)	3.4 (10.0)	
PANSS (Positive)	14.6 (4.0)	
PANSS (Negative)	10.1 (1.6)	
PANSS (General)	25.6 (4.9)	
PANSS (total)	50.3 (8.7)	
Length of illness	17.4 (11.4)	
CPZ mean dosage	469.9 (348.7)	

*p<0.05

- P223 figure title was “Figure 4.1 Implicit semantic priming” changed to “Figure 4.1 Implicit semantic priming (standard error displayed).
- P276, line 13 change “fluency output is reversed” to “fluency output is often reversed”
- P276, line 15 insert “although this is not always the case (Laws, et al., 2010)”

Laws, K.R, Duncan, A, & Gale, T.M. (2010). 'Normal' semantic-phonemic fluency discprepancy in Alzheimer's disease? A meta-analytic study. *Cortex, 46*(5), 595-601. doi: doi: 10.1016/j.cortex.2009.04.009

- P281, starting line 15 currently reads “Diagnosis was confirmed using the Structured Clinical Interview Diagnostic (SCID) (First et al., 1997).”
- P283, line 15 insert “Correlations were run with these symptoms because the literature suggests that negative symptoms reduce fluency output (Allen et al. 1993) that delusions can impact on fluency performance (Rossell, et al. 1999) and that thought disorder can affect fluency performance (Goldberg et al. 1998).”

Allen, H.A., Liddle, P.F., & Frith, C.D. (1993). Negative features, retrieval processes and verbal fluency in schizophrenia. *The British Journal of Psychiatry, 163*, 769-775.

Rossell, S. L., Rabe-Hesketh, S., Shapleske, J., & David, A. S. (1999). Is semantic fluency differentially impaired in schizophrenic patients with delusions? *Journal of Clinical and Experimental Neuropsychology., 21*(5), 629-642.

Goldberg, Aloia, M.S, Gourovitch, M.L, Missar, D, Pickar, D, & Weinberger, D.R. (1998). Cognitive Substrates of Thought Disorder I: The Semantic System. *American Journal of Psychiatry, 155*(1671-1676).

- P284, line 13 insert “Controlling for age did not significantly alter the fluency results.”

- P300, line 11 delete "This cognitive battery includes both classic and new neuropsychological measures designed to tease out the effects of lower order cognitive skills from EF. "
- P300, line 11 delete insert "Two well-known tasks (the Stroop and the Trails task) are included and altered to incorporate additional components designed to parcel out the effects of lower order cognitive skills from EF."
- P320 line 1 insert "Participants included the same 42 schizophrenia participants from chapter 6 (see page 284, Table 6.1 for demographic details of the schizophrenia group)."

Errata

- P173 line 16 change "Table 1.2" to "Table 2.3"
- P221 line 15, "Table 1" changed to "Table 4.1"
- P43, line 10 "(Hutton, et al. 1998; Joyce, Collinson, & Crichton, 1996)" changed to "(Hutton, et al. 1998; Joyce, Collinson, & Crichton, 1996; Leung et al. 2011)"
  Leung, Meikei, Cheung, Charlton, Yu, Kevin, Yip, Benjamin, Sham, Pak, Li, Qi, . . . McAlonan, Grainne. (2011). Gray Matter in First-Episode Schizophrenia Before and After Antipsychotic Drug Treatment. Anatomical Likelihood Estimation Meta-analyses With Sample Size Weighting. *Schizophrenia Bulletin, 37*(1), 199-211. doi: 10.1093/schbul/sbp099
- P47, line 12 change "While these batteries" to "while such tests"

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LIST OF TABLES

LIST OF FIGURES

PUBLICATIONS AND PRESENTATIONS DURING PHD CANDIDATURE

PEER REVIEW PUBLICATIONS

1. **Neill,** E, Rossell, S.L., MacDonald, S., Joshua, N., Jensen, N & Morgan, C.J.A (2011) Using ketamine to model semantic deficits in schizophrenia. *Journal of Clinical Psychopharmacology*, 31(6): 690-697 (*IF=4.9*). (As presented in Chapter Two).

2. **Neill,** E & Rossell, S.L (2013) Comparing implicit and explicit semantic access of direct and indirect word pairs in schizophrenia to evaluate models of semantic memory. *Psychiatry Research* (In Press 23.12.12). (As presented in Chapter Four).

3. Stefanovic, A, Roiser, J.P, Joshua, N.R, **Neill, E,** O'Regan, A, Morgan, C.J.A, Curran, H.V. & Rossell, S.L. (2010). Modulated prefrontal BOLD response during a semantic priming task is associated with delusions in schizophrenia. *Psychological Medicine* (in submission, 20% contribution)

PAPERS IN REVIEW

1. **Neill,** E & Rossell, S.L (2013) Category fluency in schizophrenia research: Is it an executive or semantic measure? *Cognitive Neuropsychiatry* (Final edits: as presented in Chapter Six).

2. **Neill,** E & Rossell, S.L (2013) Executive functioning in Schizophrenia: The result of impairments in lower order cognitive skills? *Schizophrenia Research* (Under review: as presented in Chapter Seven).

3. **Neill,** E & Rossell, S.L (2013) Investigating word association in a schizotypy sample: Contrasting implicit and explicit processing. *Cognitive Neuropsychiatry* (Under review: as presented in Chapter Three).

PUBLISHED CONFERENCE PROCEEDINGS

1. **Neill, E** & Rossell, S.L (2007). The ketamine model of schizophrenia and semantic memory. In Joyce PR (ed), *Australian and New Zealand Journal of Psychiatry (ASPR Scientific Meeting)*, Vol 41(2). Melbourne, Australia: Informa Healthcare. (100% contribution)

2. **Neill, E.** & Rossell, S.L. (2008). Do semantic deficits underlie delusions? The Australian Society for Psychiatric Research 2008 conference, *Australian and New Zealand Journal of Psychiatry*, 42 (3) A56l. (20% contribution)

3. **Neill, E** & Rossell, S.L (2012). The contributions of lower order cognitive skills to executive function performance in schizophrenia. *Front. Hum. Neurosci. Conference Abstract: ACNS-2012 Australasian Cognitive Neuroscience*

Conference. doi: 10.3389/conf.fnhum.2012.208.00190 Received: 25 Oct 2012; Published Online: 17 Nov 2012. (100% contribution)

CONFERENCE POSTER PRESENTATIONS

1. **Neill, E.** & Rossell, S.L (2007). The ketamine model of schizophrenia and semantic memory. *The Australian Society for Psychiatric Research, December, Melbourne, Victoria* (100% contribution)

2. **Neill, E** & Rossell, S.L. (2008). Do semantic deficits underlie delusions? *10th Biennial Australasian Schizophrenia Conference, October, Lorne, Victoria* (20% contribution)

3. **Neill, E** & Rossell, S.L (2009). The ketamine model of schizophrenia and semantic memory. *World Federation of Societies of Biological Psychiatry, June, Paris, France* (100% contribution)

4. **Neill, E** & Rossell, S.L (2010). Ketamine as a model of semantic and executive deficits in schizophrenia. *The Australian Society for Psychiatric Research 2010 conference, December, Sydney, New South Wales* (100% contribution).

5. **Neill, E** & Rossell, S.L (2012). Comparing semantic function in schizophrenia to the analogue models of ketamine and high schizotypy. *Central Clinical School, December, Melbourne, Victoria* (100% contribution)

6. **Neill, E** & Rossell S.L (2011). Comparing two analogue models of schizophrenia on the same semantic battery. *Australian Cognitive Neuroscience Society Conference, December, Sydney, New South Wales* (100% contribution)

7. **Neill, E** & Rossell, S.L (2012). Comparing semantic function in schizophrenia to the analogue models of ketamine and high schizotypy. *Australasian Society Psychiatry Research, December, Perth, Western Australia* (100% contribution)

8. **Neill, E** & Rossell, S.L (2012). Executive dysfunction in schizophrenia: a circumscribed deficit or the result of lower level cognitive impairments? *Australasian Cognitive Neuroscience Society, December, Brisbane, Queensland* (100% contribution)

CONFERENCE ORAL PRESENTATIONS

1. **Neill, E.** & Rossell, S.L. (2008). Do semantic deficits underlie delusions? The Australian Society for Psychiatric Research, *December, Australian and New Zealand Journal of Psychiatry, Newcastle, New South Wales* (20% contribution)

2. **Neill, E** & Rossell, S.L (2009). The ketamine model of schizophrenia and semantic memory. *The Australian Society for Psychiatric Research, December, Canberra, Australian Central Territory* (100% contribution).

3. Stefanovic, A., Roiser, J.P., Joshua, N.R., **Neill, E.,** O'Regan, A., Morgan, C.J.A., Curran, H.V. & Rossell, S.L. (2009). Modulated Prefrontal BOLD Response during a Semantic Priming Task is Associated with Delusions in Schizophrenia. *The Australian Society for Psychiatric Research, December, Canberra, Australian Central Territory*. Oral presentation delivered by Susan L. Rossell (20% contribution).

4. **Neill, E.** (2010). Disentangling executive from lower level cognitive deficits in schizophrenia. *Monash Alfred Psychiatry Research Seminar, August, Melbourne, Victoria* (100% contribution).

5. **Neill, E** & Rossell, S.L (2010). The ketamine model of schizophrenia and semantic memory. *27th International Congress of Applied Psychology, July, Melbourne, Victoria* (100% contribution).

6. **Neill, E.** & Rossell, S.L (2010). Using ketamine to model semantic deficits in schizophrenia. *Australian Cognitive Neuroscience Conference, November, Melbourne, Victoria* (100% contribution).

7. **Neill, E.** & Rossell, S.L (2010). Acute ketamine administration as a model for semantic and executive deficits in schizophrenia. *Cognitive Neuropsychiatry Symposium, Australian Cognitive Neuroscience, December, Melbourne, Victoria* (100% contribution).

8. **Neill, E** & Rossell S.L (2011) Implicit and explicit semantic memory in persons with high schizotypy. *6th Australian Cognitive Neuropsychology and Cognitive Neuropsychiatry Research Forum, August, Sydney* (100% contribution).

9. **Neill, E.** & Rossell, S.L (2012). Category fluency in schizophrenia research: Is it an executive or semantic measure? A new approach. *Australasian Society Psychiatry Research, December, Perth, Western Australia*. (100% contribution)

10. **Neill, E** & Rossell, S.L (2012). Does category fluency measure executive or semantic function in schizophrenia: A novel approach. *December, Central Clinical School, Melbourne, Victoria*.

ABSTRACT

Schizophrenia is associated with significant cognitive impairments. Current treatments for schizophrenia are limited, especially for cognitive symptoms. Cognitive remediation is a new and interesting possible adjunct to traditional treatment options. However, before cognitive remediation can be truly successful we must improve and expand upon our current understanding of cognitive deficits in schizophrenia.

There is evidence that two areas of cognition are particularly impaired in this group: semantic memory and executive functioning. This thesis will focus on these two areas of cognition. The current investigation of semantic memory function focused on a comparison between implicit and explicit semantic access as this has not been examined. Further, due to the large number of schizophrenia analogue studies investigating semantic function, this implicit/explicit divide was also investigated using ketamine and a high schizotypy group.

The second half of the thesis included an investigation of the relationship between executive functions and other areas of cognition. Chapter Six investigated the relationship between executive functions and semantic memory on the commonly used semantic fluency task. Chapter Seven examined the relationship between executive functions and lower order cognitive skills on the Stroop and Trails tasks from the Delis Kaplan Executive Function System test battery.

The semantic chapters suggested that in terms of reaction time and error data, semantic memory impairments mirror those seen in episodic memory: that is, there was intact implicit function and impaired explicit function. The most interesting finding, however, was that semantic priming appears to be a special case; there is evidence for impaired implicit priming in the face of intact explicit priming. In terms of the two analogue studies, schizotypy appeared to provide a good model for the semantic deficits seen in schizophrenia. Ketamine on the other hand, appeared to model access deficits but is unable to model the storage deficits that have been found in schizophrenia.

In terms of executive results, the fluency chapter suggested that semantic fluency is an appropriate measure of semantic memory in schizophrenia. When the contributions of lower order cognition were examined with regards to performance on the Stroop and Trails task, it appeared that reaction time performance was totally dependent on the lower order skills of motor speed, reading speed and visual planning. Only error data appeared to capture the contributions of pure executive function skills.

In terms of contributing to cognitive remediation, the implicit/explicit results are at too early a stage to be considered. They do, however, suggest that further research in this area is needed. The finding that executive performance is highly reliant on lower order skills suggests that these lower order deficits must be addressed in remediation before executive dysfunction can be addressed. Further, given the support for the semantic fluency task as a measure of semantic memory in schizophrenia, it would seem

to be an appropriate screening tool that might be used to assess function prior to the implementation of a cognitive remediation program.

GENERAL DECLARATION

In accordance with Monash University Doctorate Regulation 17 Doctor of Philosophy regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 1 original paper published in peer reviewed journals, 1 original paper in press and 3 original papers in the review process. The core theme of the thesis is the relationship between cognition and psychosis. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Monash Alfred Psychiatry Research Centre under the supervision of Professor Susan L. Rossell and Professor Paul Fitzgerald.

Thesis chapter	Publication title	Publication status	Nature and extent of candidate's contribution
Two	Using ketamine to model semantic deficits in schizophrenia	Published 2011	70%
Three	Investigating word associations in a schizotypy sample: contrasting implicit and explicit processing	Returned for revision	70%
Four	Comparing implicit and explicit semantic access of direct and indirect word pairs in schizophrenia to evaluate models of semantic memory	In Press 2012	80%
Six	Executive functioning in Schizophrenia: The result of impairments in lower order cognitive skills?	Returned for revision	80%
Seven	Category fluency in schizophrenia research: Is it an executive or semantic measure?	Returned for revision	90%

I have included the contents of the publications in the relevant chapters with additional information. The publications are included in their submitted form in the appendices. This method has allowed me to generate a consistent presentation within the thesis.

Signed: [redacted] **Date: 12/01/13**

INTRODUCTION

The theme throughout this thesis was a desire to better understand the cognitive deficits associated with schizophrenia. This is a worthy avenue of investigation conventional drug and talk therapies are proving to be limited in their application (Dickerson, 2000; Lieberman et al., 2005). Partly, it seems, that this is due to a failure in their ability to ameliorate the cognitive deficits associated with this illness (Meltzer, Park, & Kessler, 1999; Rector & Beck, 2001). A greater understanding of the cognitive deficits associated with schizophrenia will provide data which will therefore inform the development of cognitive remediation programs to add to our battery of treatment choices for this group.

The following introductory paragraphs are included to provide the reader with an understanding of the choices made in this thesis with regards to (1) the areas of cognition chosen for investigation (2) the manner with which each area of cognition was investigated and (3) the decision to examine analogue models of schizophrenia.

The literature shows that schizophrenia is associated with deficits in almost all areas of cognition (Heinrichs & Zakzanis, 1998; Meltzer & McGurk, 1999). There is some suggestion however, that executive function and memory are particularly impaired and further, that they are both predictive of functional outcome (Green, Kern, Braff, & Mintz, 2000).

With regards to executive function, whilst the presence of impairment in this area is well established, the nature of the deficit is still unclear. There is some confusion about whether executive deficits reflect a specific problem in higher level thinking or whether this dysfunction is, in fact, the

result of deficits in lower order processes, which can then create a difficulty in higher level thinking. It was therefore an aim of this thesis to investigate whether lower order deficits do in fact determine executive functioning. As a subsection of this investigation, a commonly used semantic task, the semantic fluency task, was investigated. This task is heavily relied upon to make conclusions about semantic function in schizophrenia. There is evidence however, that this task is confounded by its mutual reliance on executive skills. Therefore, in the spirit of breaking down the relationship between executive functions and other cognitive skills, this investigation was included.

With regards to memory function, there is already a large well established literature concerned with episodic memory deficits in this group (Rushe, Woodruff, Murray, & Morris, 1999; Toulopoulou, Rabe-Hesketh, H, Murray, & Morris, 2003). Further, cognitive strategies for dealing with episodic deficits are already available in cognitive remediation packages (Dickinson et al., 2009). Semantic memory has also been investigated in schizophrenia however; it is somewhat limited in its scope. For example, there is very little research available examining the differences in implicit and explicit semantic function in schizophrenia in detail. That is, whilst there is some evidence for deficits in each area, no single paper has actually compared implicit and explicit access in the same study sample. As such, one chapter of this thesis was concerned with investigating implicit and explicit semantic function in a single schizophrenia group.

Another two chapters of this thesis examine and evaluate the use of analogue models in their ability to mimic the semantic deficits and psychotic symptoms associated with schizophrenia. It was determined that this was a valuable addition to this thesis as the number of publications now relying on analogue models to make comment on the semantic deficits in schizophrenia is growing. Particularly

those studies using the ketamine (Adler, Goldberg, Malhotra, Pickar, & Breier, 1998; Curran & Morgan, 2000; Morgan, Mofeez, Brandner, Bromley, & Curran, 2004; Morgan, Mofeez, Brandner, Bromley, & Curran, 2004) and the schizotypy analogue models (Johnston, Rossell, & Gleeson, 2008; Morgan, Bedford, & Rossell, 2006; Moritz, Andresen, Naber, Krausz, & Probsthein, 1999; Niznikiewicz et al., 2002; Pizzagalli, Lehmann, & Brugger, 2001). It is time that the validity of these models in mimicking semantic deficits was assessed.

The thesis is not presented in the order summarised here. Rather, it is presented in chronological order of my candidature, that is, beginning with an investigation of the ketamine model, (Chapter Two) followed by the schizotypy model, (Chapter Three) then the schizophrenia study using the same semantic tasks (Chapter Four). Finally, the two analogue models were compared to the schizophrenia group in Chapter Five. The next section of the thesis was concerned with executive function. Chapter Six was an examination of a commonly used semantic task, semantic fluency, which has been proposed to be confounded by executive functions. Chapter Seven was an examination of the contributions of lower order cognitive skills to executive performance. The final empirical chapter (Chapter Eight) is an examination of the relationship between semantic and executive skills to psychosis symptoms. This is followed by a short concluding chapter (Chapter Nine).

CHAPTER 1: SCHIZOPHRENIA: SYMPTOMS AND COGNITION

1.1 Psychosis

1.1.1 What is Psychosis?

Psychosis is a term that has been in existence for over 100 years. However, there is some confusion as to who first introduced this concept. Some authors credit Canstatt in 1841 (Burgy, 2008, p. 59) while others suggest that the terms 'psychosis' and 'psychopathy' were coined by Feuchtersleben in 1845 (Beer, 1996). Feuchtersleben used the term to describe diseases of personality. Diseases which he believed were not confined to the mind but were the result of abnormalities in the mind and body and their relationship with one another. The term psychosis was used in various ways in the years following. Flemming in 1859 used the term psychosis to refer to mental illness in general; and Kraeplin was responsible for differentiating between psychosis (referring to a lack of insight) and psychopathy (a personality trait) (Beer, 1996).

Currently, psychosis describes a state shared by a number of different mental illnesses. In the International Classification for Diseases version 10 (ICD-10) it is defined as:

" the presence of hallucinations, delusions, or a limited number of severe abnormalities of behaviour, such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behaviour." *(ICD-10, 1990, p. 10)*

In the Diagnostic and Statistical Manual of Mental Disorders version 4 (DSM-IV-TR) psychosis is defined differently depending on the specific disorder described. For the most well recognised psychotic disorders (schizophreniform disorder, schizophrenia and schizoaffective disorder)

psychosis refers to experiencing delusions, hallucinations, disorganised speech/behaviour or catatonia (2000).

In the current thesis, features of psychosis were examined using analogue and schizophrenia studies. In Chapter Two, ketamine was given to a group of healthy individuals to induce psychotic symptoms. In Chapter Three, a sample of healthy participants was divided into a high and low schizotypy group (alternatively referred to as psychosis proneness) and Chapter Four, Five and Six involved the testing of schizophrenia participants.

1.1.2 What is Schizophrenia?

Schizophrenia is a devastating illness affecting approximately 1% of the population. Its causes are unknown although there does appear to be a genetic influence involved as the chance of developing the illness increases tenfold for those individuals who have a first degree relative with schizophrenia (Chang, Chen, & Liu, 2002,1010), and reports suggest a 40-50% concordance rate between identical twins (Tsuang, 2000) and a meta-analysis of 12 twin studies estimated heritability in liability to schizophrenia at 81% (Sullivan, Kendler, & Neale, 2003). It is not simply a case of genetics, however, as many individuals with schizophrenia do not have a first degree relative with the illness (Weiser, Davidson, & Noy, 2005). There is also evidence that stressful life events can play a role in the development of schizophrenia including drug and alcohol abuse, poor premorbid cognitive and social functioning, urban living and immigration (Weiser et al., 2005).

The most commonly used criteria for the diagnosis of schizophrenia are outlined in the DSM–IV–TR (2000). The symptoms that may be present in schizophrenia include delusions, hallucinations,

disorganised speech, grossly disorganised or catatonic behaviour or negative symptoms such as affective flattening, alogia or avolition. Two of these symptoms must be present for a significant portion of a month, interfering with at least one of three spheres of life: hygiene, work or social interaction. These disturbances must continue for at least six months, although they may be attenuated for part of this time. The individual must not exhibit symptoms more in line with schizoaffective disorder, bipolar disorder or a personality disorder. Five subtypes of schizophrenia are identified in the DSM. These include paranoid schizophrenia, characterised by prominent delusions, and/or auditory hallucinations with relatively intact intellect. The disorganised type is defined by disorganised speech and behaviour and often inappropriate affect. The catatonic type includes marked motor disturbance with such symptoms as mutism, excessive or lack of movement, peculiar movements and echolalia. An undifferentiated type is also included in the DSM, and is defined by symptoms indicating schizophrenia but a pattern of symptoms that cannot be easily classified as paranoid, disorganised or catatonic. Finally, a residual subtype describes those individuals who have experienced at least one episode of schizophrenia but whose clinical picture does not include prominent positive features. Negative features, such as flattened affect and poverty of speech are often still present. Any positive symptoms that do remain are attenuated. These subtypes are referred to less and less in the research literature. One reason is that even within these subtypes there is substantial variation. This variation in turn adds to heterogeneity in the literature. To avoid this problem, researchers are now taking a more symptom based approach (Costello, 1992). In the current thesis, the focus is on the symptoms of delusions and thought disorder as these have been linked to specific cognitive impairments.

1.2 Schizophrenia and Cognition

Cognitive impairment is a core feature of schizophrenia (Green, 2006) with some authors suggesting that these deficits should be included in the criteria for diagnosis (Keefe, 2008). Further, these impairments have been linked to functional outcome (Bowie & Harvey, 2006; Green, 2006) in particular, function has been closely linked to memory and executive skills (Green et al., 2000; Kuperberg & Heckers, 2000). Further, cognitive deficits remain between psychotic episodes and are not ameliorated by antipsychotic medication (Green, 2006) (although there is some suggestion of mild improvement using atypical medications). It is therefore important to fully understand the nature of these impairments.

Some studies suggest that schizophrenia is associated with intellectual decline (Seidman, Buka, Goldstein, & Tsuang, 2006) with authors demonstrating that cognitive impairment is present in around 75% of schizophrenia patients (O'Carroll, 2000). Research suggests that cognitive problems precede the development of frank psychosis with a recent meta-analysis reporting that individuals who went on to develop psychosis had a significantly lower premorbid IQ (half a standard deviation) compared to those who did not go on to develop psychosis (Woodberry, Giuliano, & Seidman, 2008). There is contradictory evidence regarding the stability of cognitive impairment in schizophrenia over the life span. An older meta-analysis reported a decline in IQ over time (Aylward, Walker, & Bettes, 1984), confirmed by a more recent research study that examined data from the 'prospective, longitudinal, National Collaborative Perinatal Project', they measured the IQ's of children aged seven and re-tested them twenty eight years later. They found that children who went on to develop schizophrenia were impaired at seven and demonstrated a decline in IQ compared to those who did not develop psychosis (Seidman et al., 2006). Other research disagrees dramatically going so far as to describe intellectual

decline in schizophrenia as a myth (Russell, Munro, Jones, Hemsley, & Murray, 1997). Still others suggest that a percentage of individuals with psychosis will decline over time, some are premorbidly impaired and remain unchanged and others have no premorbid impairment and no decline (Weickert et al., 2000).

The cognitive profile of schizophrenia is characterised by deficits in almost all areas of cognition including: processing speed, attention, memory, executive functions and social cognition (Green, 2006). There is further contention regarding the pattern of cognitive impairment. While some authors simply describe cognitive impairment as being wide spread across domains (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005) there is a large body of evidence suggesting that more serious deficits occur in memory (Heinrichs & Zakzanis, 1998; McKay et al., 1996; Saykin et al., 1991) and/or executive functions (Barch, Braver, Carter, Poldrack, & Robbins, 2009; Kremen, Seidman, Faraone, & Tsuang, 2001; McKay et al., 1996). The research in this area have ascertained that these disproportionate deficits cannot be attributed to drug treatments (Saykin et al., 1991), distraction due to symptoms including hallucinations (Laws & McKenna, 1997), premorbidly impaired intellect (Hori et al., 2008) or poor motivation (Goldberg, Weinberger, Berman, Pliskin, & Podd, 1987). The executive element is complicated by the fact that complex tasks are often regarded as executive (particularly those associated with attention) and an increase in task complexity is associated with an increase in the utilisation of other non-executive skills (Keil & Kaszniak, 2002). In addition, given the well documented deficits in lower order cognitive skills, defining the precise nature of executive difficulties can be problematic, as poor lower order processing clearly impacts on the efficiency of executive skills.

The significance of the cognitive deficits found in psychosis have led some authors to suggest that schizophrenia might be better defined by the presence of stable cognitive deficits than by psychotic symptoms (which fluctuate significantly over times) (Elvevag & Goldberg, 2000). They have further stated that cognitive impairments are at the core of all the dysfunction associated with schizophrenia.

At this stage, to move forward in our understanding of the role of cognition in the presentation of schizophrenia, it is necessary to search for or identify patterns of cognition that are not simply the result of the generalised cognitive deficit often seen in this group (Hemsley, 2005). It is therefore useful to look for areas where performance is intact, to search for cognitive skills that might be enhanced (possibly suggestive of compensation) to find areas of more severe impairment or to identify relationships between specific cognitive skills and specific symptoms of schizophrenia. In the current thesis, by collecting neuropsychological data from multiple domains, areas of intact performance may be identified. By examining semantic priming (an area found to be enhanced in some situations), and both executive and memory deficits (areas thought to be most significantly impaired), and by exploring the relationship between these cognitive abilities and symptoms, this thesis will attempt to provide information that will enhance our understanding of the relationship between psychotic symptoms and cognition.

1.2.1 Executive Function (EF)

One of the earliest and most influential investigators of EF was Alexander Luria (1902-1977). He developed theory based on the clinical evidence he gathered from working with neurological and neurosurgical cases relating to damage sustained during the second World War (Tupper, 2006). Luria was one of the first to point out the unique importance of the frontal lobe in EF's suggesting that they

behaved as a sort of tertiary association area of the brain as a whole; a statement that has led to the view that EF's are the most significant of brain functions (Stuss & Benson, 1986).

Despite many years of EF research, there are still inconsistencies with regard to determining what skills contribute to EF. One definition suggests that it includes "skills that allow one to organise behaviour in a purposeful, coordinated manner, and to reflect on or analyse the success of the strategies employed" (Banich, 2004, p. 391). Others have broken it down into the components of volition, planning, purposeful action and effective performance (Lezak, Howieson, & Loring, 2004). The specific skills thought to be included are often classified differently depending on the author. Many authors have identified similar skills for example, Lezak's component of 'volition' is similar to the concept of 'initiation' by Stuss and Benson (1986) and 'generation' by Keil and Kaszniak (2002). The concept of 'planning' by Lezak is often used synonymously with the term 'organisation' (Sohlberg & Mateer, 2001) and the concept of 'purposeful action' has been described as 'execution' (Luria, 1966) and 'task persistence' (Sohlberg & Mateer, 2001). The concept of 'self-monitoring' by Luria (1966) is also similar to the concept of 'awareness' by Sohlberg and Mateer (2001). In addition, the skill of mental flexibility is synonymous with switching or set shifting and reasoning and inference making are also used interchangeably. Finally, working memory is also considered by many authors to be a measure of EF (Keil & Kaszniak, 2002) with some executive theories focusing solely on this skill (Baddeley & Hitch, 1974). The confusion with regard to working memory is evident even within this thesis. For example, working memory tasks have been included in the current executive battery but in Table 1.4 they are referred to as 'other skills' rather than EF's because many authors consider them such. Further, in Table 1.3 which includes EF tasks, the different skills are sometimes lumped together (planning and problem solving for instance) because tests rarely assess one without the other. It is

difficult to find an all-encompassing, agreed upon, definition of executive functioning. Generally speaking though, executive functioning describes higher level complex thinking skills (Lezak et al., 2004) or control functions (Stuss & Alexander, 2000).

1.2.1.1 Theories of Executive Functioning

Some theorists have suggested that these EFs are unitary and stem from the same skill set, while others suggest that EFs are separable and independent (Jurado & Rosselli, 2007). In the early days of classification, it appeared as though EF's were highly related. Recent data has suggested that there is some basis for this idea, given that significant positive correlations have been found between many EF tests (Duncan, Emslie, Williams, Johnson, & Freer, 1996). Those authors who believe in division between the skills report that there are brain injured patients who demonstrate poor performance on some executive tasks but intact performance on others (Godefroy, Cabaret, Petit-Chenal, Pruvo, & Rousseaux, 1999). Miyake (2000) found that different EFs correlate only moderately with one another suggesting some cross over but also that there is significant independence. In addition, evidence shows that EF overlaps significantly with general intellectual abilities suggesting that these functions are highly dependent on other cognitive domains to function (Obonsawin et al., 2002). Further evidence finds this to be true for some EFs while for others, it appears that lower level cognitive skills contribute very little (inhibition and switching) (Friedman et al., 2006). One of Luria's greatest contributions to neuropsychology was his proposal that the brain could be broken down into three major components. (1) The arousal/attention areas (brain stem) which are the lowest level relating to alertness and tone. Damage to this arousal area is associated with slowed and inadequate physical (psychomotor retardation) and mental skills (hypomania). (2) Skills that relate to the processing and storing of sensory information (including primary, secondary and tertiary association areas). This area is

important in the processing, integration and comprehension of incoming sensory information and for basic cognitive skills like memory and finally (3), EFs (thought to reside in the frontal lobes). The distinction of EF from other cognitive domains has led researchers to explore the EF as a separate set of cognitive skills (Luria, 1966; Stuss & Benson, 1986).

There have been numerous theories put forward to explain the role of EF and its relationship to other brain functions including the feedback system proposed by Pribram (1960) the corollary discharge theory of Teuber (1964), Nauta's neuroanatomical model (1971) and Damasio's anatomical-functional model (1979) (Stuss & Benson, 1986).

There are more theories of executive function than can be practically and usefully discussed in this chapter. Many of these theories overlap significantly and as such, just some of the main theories are discussed here and summarised in Table 1.1.

Table 1.1 *Theoretical Executive Skills*

Luria (1966)	Baddeley & Hitch (1974)	Lezak (1983)	Norman & Shallice (1986)	Stuss & Benson (1986)	Delis, Kaplan & Kramar (2001)
Anticipation	Central Executive	Volition	Supervisory attentional	Initiation	Inhibition
Planning	Phonological loop	Planning	Contention scheduling	Planning	Planning
Execution	Visualspatial scratchpad	Purposive action		Sequencing	Mental flexibility/ switching
Self-monitoring		Effective performance		Regulation	Working memory
				Organisation	Problem solving

1.2.1.2 Executive Functioning and the Frontal Lobes

Another area of importance in any discussion of EFs relates to the neuroanatomical locations of these functions. For many years, the term EF was used synonymously with frontal functioning (Stuss & Alexander, 2000). There is now ample evidence that there is a complex relationship between the frontal lobes and other brain regions required to bring about these complex higher order skills (Alvarez & Emory, 2006). Research has identified a number of circuits throughout the brain that contribute to EF. The three EF circuits involve, but are not limited to, the frontal lobes and include (1) the dorsolateral prefrontal circuit (2), the orbital frontal circuit and (3) the anterior cingulate circuit. All three circuits begin in the frontal lobes but project to parts of the basal ganglia (including globus pallidus, substantia nigra, caudate, accumbens, and putamen) and the limbic system and both the hypothalamus and thalamus. The circuits are then closed by returning to the frontal lobes (Tekin &

Cummings, 2002). Deficits in the brains areas involved in the dorsolateral circuit are associated with poor planning/organisation, poor memory search strategies, stimulus bound behaviour, impaired set shifting and verbal manual dissociation. Damage to the lateral orbital prefrontal circuit can result in personality change, environmental dependency, mood disorders and obsessive compulsive behaviour. Finally deficits in the anterior cingulate circuit can lead to poor motivation and poor inhibition (Mega & Cummings, 1994). In addition to these three loops, there is evidence that the integrity of the cerebellum is important to EF (Bellebaum & Daum, 2007) with imaging research suggesting that there is a cotrico-ponto-cerebellar network which has many connections to the frontal cortex (Schweizer et al., 2008). Further, clinical evidence including the effects of tumours (Karatekin, Lazareff, & Asarnow, 2000) and cerebellar haemorrhage (Schweizer et al., 2008), has demonstrated the existence of the relationship between the cerebellum and EFs. So finally, in the words of Mack and Patterson (1995, p. 564) "Although defective EF is certainly an important consideration of frontal lobe involvement, it is not logically necessary to conclude that executive deficits arise exclusively from damage to the frontal areas of the brain."

1.2.1.3 Relationship between executive functions and lower level cognitive skills

For many executive skills to function, lower level cognitive skills need to be intact. There is ample evidence that EF relies heavily on lower level skills. For example, studies have shown that executive functioning is reliant on processing speed (see Figure 1.1) (Savla et al., 2010).

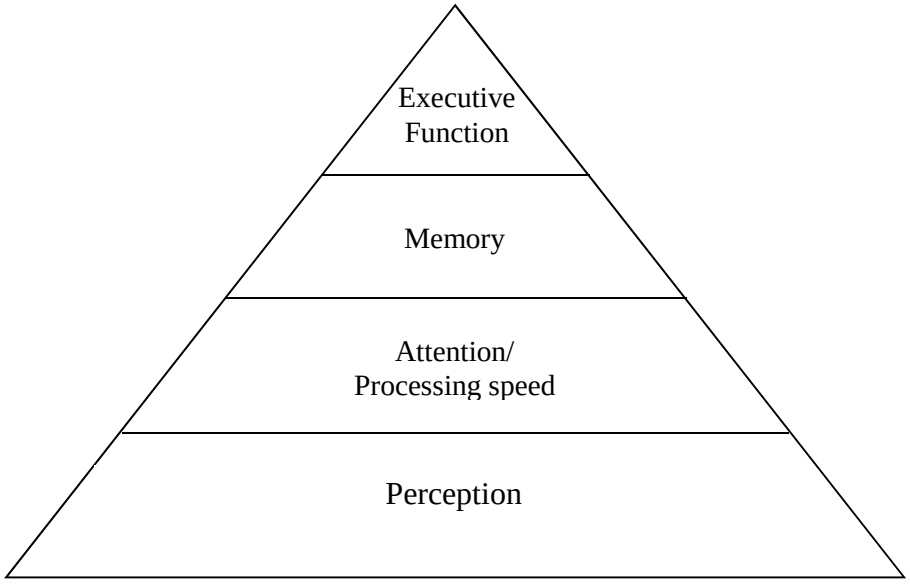

Figure 1.1 Hierarchy of Cognition

1.2.1.4 Executive Function Measures

There are many different measures that are purported to tap into EF. Table 1.3 contains a list of some of the major executive domains and the most popular tests proposed to tap into those functions. An examination of Table 1.3 demonstrates that many of these tasks tap into more than one executive domain. For example, the traditional Stroop task requires initiation/verbal generation and inhibition.

Table 1.2 *Executive Domains and their Suggested Tasks*

Executive Domain	**Task Name**
Planning/ Organisation/ Prediction/ Problem Solving	Rey Osterrieth Complex Figure Maze Tasks Animals by Size Tower of London/Hanoi Brixton
Volition/ Initiation/ Generation/ Inhibition	Stroop Go-No Go tasks Fluency tasks (phonemic/semantic) Five Point Test
Switching/ Set Shifting/ Mental Flexibility	Trails B D-Kefs Stroop Alternative Uses Tests Category Test

* Effective performance /monitoring is required for successful completion of too many tasks to list
* Relationships between tasks and domains are confirmed by Lezak (2004)

Another problem that must be considered in interpreting output from executive tasks is that successful completion of such tasks requires (1) intact EF and (2) intact lower level cognitive functions. Generally speaking, most cognitive tasks require intact basic perception and some degree of attention. Processing speed becomes an issue on any task that is timed and immediate memory span must be considered with any task that does not have all components written down in front of the participant (see Table 1.3 below for an outline of the executive tasks used in the current thesis and the list of necessary associated lower level cognitive skills). Some task batteries have attempted to take lower level cognitive skills into consideration in their revisions of executive tasks. One such task battery is the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001). This battery includes modified versions of some classic measures designed to separate out the different cognitive components necessary for task completion. Two such modified tasks in the D-KEFS include the Stroop and the Trails tasks. The Trail Making task modifications includes a psychomotor speed component, a

visual scanning component as well as versions that check letter and number knowledge. The Stroop includes an extra condition so that both inhibition and switching can be examined. Both the D-KEFS Trails and Stroop were included in the current thesis for this reason.

Table 1.3 *Tasks and their Reliance on Multiple Cognitive Domains*

Task Name	**Visual/Verbal Task**	**Executive Function**	**Other Cognitive Functions**
Brixton Task	Visual	• Flexibility/ Concept formation (Lezak et al., 2004)	• Working Memory (Reverberi, Lavaroni, Gigli, Skrap, & Shallice, 2005)
Stroop Task	Visual/Verbal	• Set Shifting (Lezak et al., 2004) • Inhibition (Sugg & McDonald, 1994)	• Selective Attention (Ponsford & Kinsella, 1992) • Working Memory (McCabe, Robertson, & Smith, 2005) • Processing Speed (Bugg, DeLosh, Davalos, & Davis, 2007)
COWAT/ Fluency	Verbal	• Flexibility • Planning (Lezak et al., 2004)	• Sustained Attention • Working Memory • Semantic Memory • Processing Speed (Kemper & McDowd, 2008)
Rey Complex Figure	Visual	• Planning (Lezak et al., 2004)	• Visuo-Spatial (Rapport, Dutra, Webster, Charter, & Morrill, 1995)
NAB Mazes	Visual	• Reasoning/ planning • Problem Solving (Nuechterlein et al., 2008)	• Visuo-Spatial • Processing/ Psychomotor Speed (Horton & Wedding, 2008)
Trail Making Task	Visual	• Set Shifting (Lezak et al., 2004)	• Attention • Visuo-Spatial • Processing/ Psychomotor Speed • Working Memory (Delis et al., 2001)

1.2.1.5 Executive Functioning in Psychosis

"Failure on any cognitive test conveys no information about the specificity of cognitive dysfunction if patients: are impaired on most other tests; are not examined on other tests; have low IQ; or display intellectual deterioration" (Laws, 1999, p. 10).

The suggestion that executive function is more impaired than other cognitive domains remains contentious, with some authors suggesting problems in this area are simply the result of the compounding of lower level deficits (Laws, 1999) while others suggest that executive deficits should be regarded as a hallmark of psychosis (Barch et al., 2009). What is not contentious is the finding that deficits in EF significantly predict long term functioning (Reed et al., 2002) and as such, further examination of EF deficits is required. As a result of its effect on outcome, EF is often a key element in contemporary neurocognitive models of psychosis (Savla et al., 2011). Research has suggested that problems in this area affect between 40-95% of individuals with a schizophrenia diagnosis (Velligan & Bow-Thomas, 1999). Importantly, these deficits have been found to be present at first episode of psychosis (Hutton et al., 1998; Joyce, Collinson, & Crichton, 1996) suggesting that they are not simply the result of medication. There is evidence that some cognitive problems occur during psychotic episodes but decrease when symptoms are controlled. The deficits in EF however, seem to remain stable over time (Tyson, Laws, Roberts, & Mortimer, 2004).

1.2.2 Semantic Memory

The aim of this section is to provide a background regarding theories of memory storage. This will be followed by an examination of semantic memory in terms of both structure and access. Semantic memory will receive more attention than executive function as it has been more closely tied to the occurrence of specific symptoms of psychosis including thought disorder and delusional thinking.

Semantic memory is a long term memory store. To understand the kinds of information it stores, comparisons will now be drawn between semantic and episodic long term memory. Episodic memory describes our memory for a particular event, for example, your first day at high school. This is the kind of memory that is autobiographical, containing memories specific to personal experience. It is also the type of long term memory that most people are familiar with. Semantic memory on the other hand contains information regarding more general factual knowledge (Tulving, 1972); for example, the capital of France or the year the Olympics were held in Sydney. There are a number of important differences in the way in which these two long term memory stores encode, learn and access information.

A major difference in the learning of the two memory systems is the importance of the temporal spatial timing of events and its impact on retrieval. In episodic memory, people store episodic events in a sequential way. For example, for a person to remember that an event followed another event (graduating from high school came after the first day at high school) they must experience the events in that order. Semantic type memories on the other hand may be learned out of sequence. For example, one might learn about the effect that World War II had on Europe and then later learn about the events that led up to the outbreak of that war (Tulving, 1972).

Another difference is the inferential capabilities of the two systems. Information can only be retrieved from episodic memory if it is directly stored there. The semantic system on the other hand contains information that allows the retrieval of other information that is not directly stored in memory; it allows us to make inferences. Tulving (1972) gives the example that if you learn the months of the

year in alphabetical order, ‘June’ does not follow ‘March’, however, semantic memory allows us to infer that in fact, June does follow March.

The consequences of retrieval also differ between the two systems. According to Tulving (1972) retrieval from semantic memory does not affect the structure of the semantic network but the episodic store is affected by retrieval. Theories of semantic memory since Tulving’s original hypothesis, however, suggest that access and patterns of access to the semantic store also affect retrieval with regard to the strength of relations between concepts (Collins & Loftus, 1975). In addition, Tulving suggests that access to either the semantic or the episodic system generally results in an episode being entered into the episodic memory store.

Tulving (1972) also proposes that the episodic system is more vulnerable to interference and forgetting than is the semantic system. This vulnerability is related to the time tags necessary to encode and retrieve episodic memories. Tulving proposes that because time tags are necessary, and not just additionally helpful to retrieval, then the disruption of this one feature is enough to lose access to the memory. In semantic memory on the other hand, there are many more links between concepts which render them less vulnerable to disruption.

In conclusion, Tulving (1972) proposes four main areas of difference between these two long term memory stores. First, is the nature of the stored information (autobiographical versus factual); second, is the difference in inferential ability of the stores; third, are the differences in conditions required for encoding and retrieval, and finally, the susceptibility of the stores to interference. Now that the nature of semantic memory has been clarified in comparison to the more commonly understood

episodic memory system, an examination of the theories surrounding the structure and access to the semantic memory network will be examined.

1.2.2.1 Measures of Semantic Memory

Measures of semantic memory are discussed before an explanation of the theories of semantic memory because one specific test is predominantly used to devise and examine such theories. As such, a brief list of the possible tests will be discussed culminating with a description of the semantic priming task, a pivotal task in this domain. This will then be followed by the theories that are most often assessed using this measure.

A number of neuropsychological tests measure semantic function. Many of these are tests of aphasia which not only examine language function but also semantic memory. These tasks generally require participants to recognise and name or match objects. In addition to the requirement of intact language, the semantic representation of the objects must also be functioning to complete these tasks successfully. The benefit of tests with this structure is that they generally do not put pressure on executive skills or processing speed. Semantic fluency tasks have also been use to assess semantic function (Bokat & Goldberg, 2003; Henry & Crawford, 2005). With semantic function assessed in terms of total output or cluster analysis. The problem with relying on neuropsychological tests that are not designed solely for the purpose of assessing semantic function is that they either do not tap into the problem sufficiently or they are confounded by deficits in other cognitive areas. For example, while the aphasia tasks are not confounded by executive function and processing speed requirements, they are only able to assess gross semantic disruption such as naming difficulties (especially for common words), problems which do not occur unless there is quite a severe degree of semantic impairment.

The fluency task is also problematic as a measure of semantic function with some authors arguing that it is confounded by executive and processing speed elements (Doughty & Done, 2009).

Specific individual tasks have been devised to measure semantic memory including the 'silly sentences task' (Collins & Quillian, 1969) which requires participants to ascertain the veracity of a sentence as 'true' or 'false'. A 'true' sentence would be 'canaries can fly' while a false sentence would be 'screwdrivers have jobs'. These sentences require intact semantic memory in order to recognise the falsehood of some sentences. In addition to traditional neuropsychological tests and a few individual semantic tasks, semantic batteries have been designed specifically for the purpose of assessing function of this memory system. Two such batteries include the Hodges Semantic Memory Test Battery (Hodges et al., 1992) and Pyramids and Palm Trees (Howard & Patterson, 1992). While these batteries are commonly used to assess individuals with Alzheimer's disease, in the psychosis literature, the task most commonly used is the semantic priming task. Details on how this task is constructed will be discussed later in this chapter (section 1.4) but for the purposes of understanding how this task can be used to assess the semantic system; the following brief description is provided. Typically in semantic priming, the participant is presented with one word after the other. The first word is known as the 'prime' and the second word, the 'target'. Sometimes these words are related (DOG-CAT) and sometimes they are unrelated (DOG-MANGO). The general finding is that participants are quicker to respond to pairs of words that are related, this is known as the "semantic priming effect".

1.2.2.2 Theories of Semantic Memory

The main theories of semantic memory include: spreading activation theories (SAT) (Collins & Loftus, 1975), compound cue theories (CC) (Ratcliff & McKoon, 1988) and parallel distributed

network models (PDN) (Hinton & Shallice, 1991; Masson, 1995; Sharkey & Sharkey, 1992; Sharkey, 1989, 1990). Briefly, spreading activation theories propose that semantic memory is made up of nodes, each of which represents a particular concept. When one concept is activated, access to similar concepts is facilitated. Compound cue theories suggest that when familiar concepts are seen together, they are grouped in short term memory and access semantic memory as a compound. Facilitation occurs because related concepts accessing memory as a compound offer greater familiarity than do unrelated concepts. Finally, the parallel distributed network model suggests that concepts are represented by a pattern of activation based on the features of the concept. Those items made up of similar features become facilitated for access (Plaut, 1995). None of these theories address the issue of acquisition of memory. All focus on access to this memory system (Quillian, 1968). Although these theories appear to be quite similar in nature, they make different predictions with regard to patterns of semantic priming. Each theory will now be discussed in detail.

1.2.2.3 Spreading Activation Theory

Quillian (1968) proposed one of the first accounts of a spreading activation theory (SAT) of semantic memory. SAT's are the most widely accepted accounts of semantic memory organisation and access (McNamara, 2005). Quillian developed his theory to be used as a computer simulation of semantic memory and as such, there were a number of shortcomings associated with his work. In response to criticisms, Collins and Loftus (1975) extended the theory, phrasing the work in psychological terms and correcting those proposals refuted by research. The following describes Quillian's theory and includes the corrections and extensions proposed by Collins and Loftus (1975).

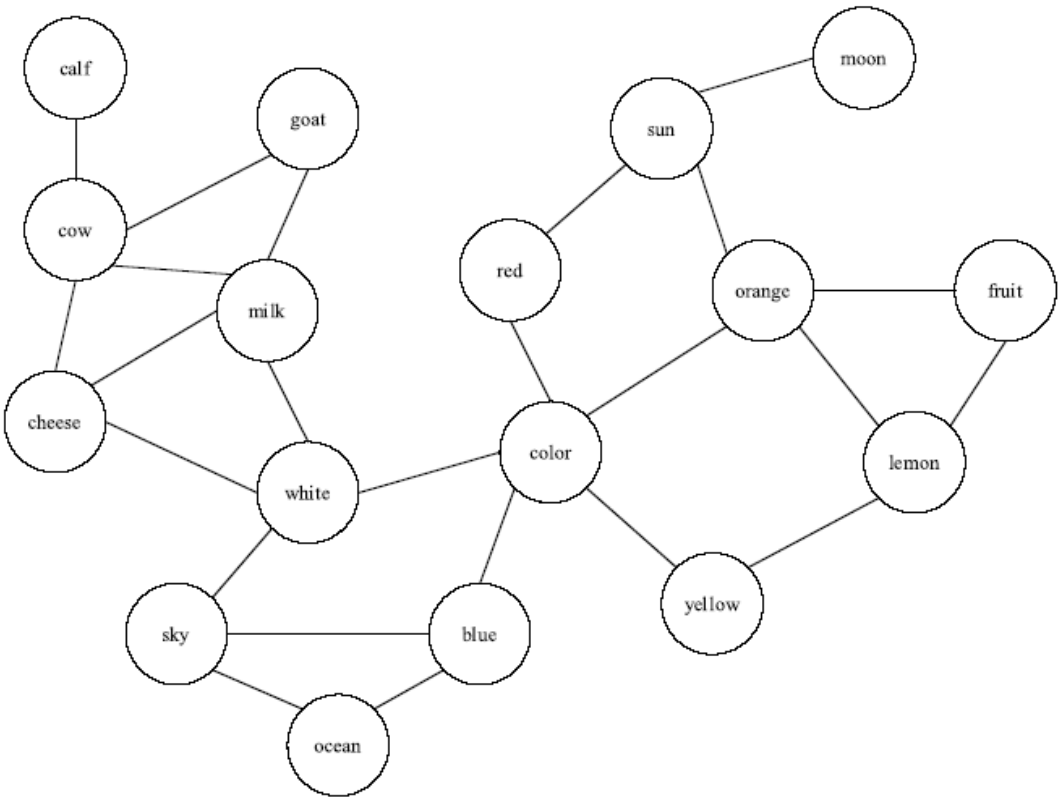

Figure 1.2 Schematic of the Semantic Network (Minzenberg, Ober, & Vinogradov, 2002)

Quillian (1968) proposed that semantic memory is made up of a series of connected conceptual nodes. Each node contains information relating to a particular concept and links connect the concept to other related concepts (for example CAT might be closely linked to DOG). When a concept is activated (comes to the attention of the individual), closely related concepts become more accessible through the process of 'spreading activation'. The spread of activation extends from the initially activated node through to those concepts related/connected to it. As a result, if one of these more accessible concepts also comes to the attention of the individual, it will be recognised or accessed more quickly than one that is unrelated because of the priming provided by the initially activated node (McNamara, 2005).

Quillian (1968) proposed that there are two separate memory networks that make up the semantic memory system including both a lexical and a semantic network. The lexical network contains the word itself whereas the semantic network contains information pertaining to the meaning of the word. Collins and Loftus (1975) extend this assumption. They proposed that the lexical network contains both orthographic and phonemic information and suggested, based on research, that the lexical network can be primed separately from, or as well as, the semantic network.

In Quillian's (1968) original theory, it was presumed that the spread of activation was unlimited in the degree to which it primed related stimuli. Research since their proposal showed that semantic memory is in fact limited (Collins & Loftus, 1975). Collins and Loftus proposed that spread of activation becomes weaker the further it gets from the initially activated node and activation and priming of nodes decreases over time as attention is given to other activities. They also suggested that whilst related nodes are primed, only one concept can be *actively* processed at a time. They extended Quillians theory by adding that the longer a concept is actively processed, the longer related concepts will remain primed. Also, when two indirectly related concepts are examined (LION - STRIPES) the point at which the two concepts intersect will be evaluated (TIGER).

According to Quillian's theory, there are two distinct types of conceptual nodes. These include 'type' and 'token' nodes. 'Type' nodes describe category titles such as VEHICLES or BIRDS whereas 'token' nodes refer to specific examples of such categories i.e. CAR or ROBIN. Quillian also assumed that semantic memory is hierarchically organised by these distinct node forms with all token nodes activated equally by the activation of their type node. Research since has indicated that this is not the

case as less commonly associated members of a category are found to produce less priming then commonly associated members. For example, following the word BIRD, PENGUIN does not produce as much priming as ROBIN. To understand how Collins and Loftus (1975) dealt with this problem, an understanding of the role of links between concepts must first be discussed.

So far, this discussion suggests that the role of links is simply to join together meaningful information. According to both Quillian (1968) and Collins and Loftus (1975) links also contain meaningful information and are essential in defining the nature of relationships between nodes. Quillian describes links as having different 'criterialities', referring to the importance of each link to the meaning of a concept. The criterialities of any pair of links between two nodes does not have to be equal. Quillian uses the example of the type node of MACHINE. He proposed that it is more critical to the meaning of TYPEWRITER that it is a MACHINE than it is to MACHINE that one sort is TYPEWRITER. Quillian also suggested five kinds of links that can exist between nodes.

1) Superordinate and subordinate links (between type and token nodes)

2) Modifier links (adjective or adverb)

3) Disjunctive sets of links (air, earth or water form a disjunctive set)

4) Conjunctive sets of links ('old, red house' requires the modifiers of house to be formed into a conjunctive set)

5) Finally, a residual class of links for those situations in which the link itself is a concept.

Collins and Loftus (1975) extended the above proposals. They suggested that links contain information pertaining to the properties of the concepts they connect, and as a result both links and conceptual nodes can be primed. Links are also described as having different degrees of accessibility

depending on how often concepts and properties of concepts are considered together. For example, the links between BIRD and ROBIN may be 'stronger' than the links between BIRD and PENGUIN because it is more usual to discuss ROBIN as a BIRD than it is to discuss a PENGUIN as a BIRD.

These are the major assumptions of the SAT; we will now turn to an examination of the compound cue theory of semantic memory. This theory was developed in response to the development of SAT's and in direct competition to this theory.

1.2.2.4 Compound Cue Model

Unlike SAT's, the compound cue model (CC) does not assume that on presentation, the prime concept immediately accesses long term memory. Instead, concepts are initially held in short term memory where they are grouped together as a compound and it is as this compound that they access long term memory (Ratcliff & McKoon, 1988). The longer pieces of information are rehearsed together, the greater the familiarity that is developed between them. In this model, the degree of relations between items is given a strength/weight rating. The rating of familiarity between an item and its most closely related items is 1.0. For less closely related items, the degree of relatedness is set at 0.2. The familiarity of a single cue is calculated as the relatedness of that cue to an image in memory multiplied by the relatedness between the context within which the cue is presented to that same image in memory. This is then summed over all images in memory to gain an overall familiarity rating. When two cues are presented together, they form a compound along with context. This information as a whole is then compared to all images in memory. Familiarity is calculated as the strength of the prime to an image in memory multiplied by the strength of the target and the context to that same image. The strength of the relationship between the prime to the image is given less weight than the

strength of the relationship between the target to the image because it is the target, not the prime, which is responded to.

Ratcliff and McKoon (1988) propose that the degree of priming is limited to two steps. This means that a word can prime its closely related concepts (one step) for example LION – TIGER and can also be primed to those concepts closely related to the concepts one step removed (two steps), LION – STRIPES, but no further. Priming for those concepts two steps removed is much weaker. This is related to the weighting of cues. As mentioned above, the target carries a heavier weighting than the prime due to the position of the target in the compound (most recent) and the more concepts that are considered before a decision can be made, the weaker the priming. The SAT suggests a similar idea but the difference lies in the fact that the CC specifies that priming can only occur within two steps.

The concept of prelexical processing is treated differently by the CC than the SAT. Prelexical processing describes the development of expectancy in response to receiving the prime, in other words, participants are able to generate possible relations to the prime. For example, on receiving the word DOG they might generate CAT, COLLAR or PET. Given the nature of the CC, the idea of prelexical processes is abandoned because according to this model, the prime and target are received together. Ratcliff & McKoon (1988) also argue that post lexical processing does not occur (checking target against prime once both have been received) because the pair are presented or accessed by the semantic system together. Neely (1991) on the other hand argues that post lexical processing might still occur using this framework.

There are many more postulations of the CC but for the purposes of this thesis, only the strongest predictions have been discussed. Next is an examination of the parallel distributed networks model.

1.2.2.5 Parallel Distributed Network Model

Masson's (1991) version of the parallel distributed network model (PDN) will be examined here. As with the compound cue model, this model was created in response to the SAT as an alternative model of semantic memory.

Masson's model is based on a Hopfield network; these computerised networks were originally designed to imitate the function of neural networks. Instead of assuming that concepts are stored in a single node, the Hopfield network adopted by Masson assumes that memory consists of a whole network of nodes and it is the pattern of activation of these nodes, rather than the activation of a single node such as with SAT's, that represent a concept. This is the fundamental difference between this model and an SAT model of semantic memory.

According to this theory, only one concept can be activated at any one time in the network. Other concepts may be partially activated if they share some of the pattern of activation in common with the activated node. It is also assumed that related concepts have a more similar pattern of activation then do unrelated concepts; Figure 2 demonstrated this. The concept of CAT and the concept of DOG are more similar to one another than they are to the concept of CHAIR. As such, their pattern of activation is more similar. When a concept is active therefore, related concepts are also partially active to the degree that they share a common pattern of activation.

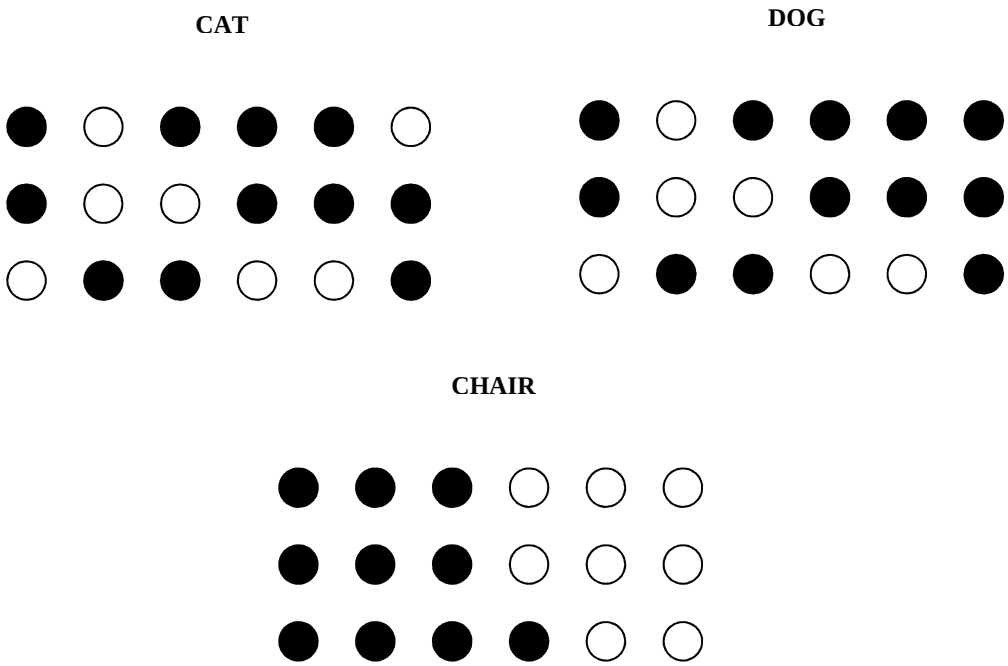

Figure 1.3 Schematic of a Hopfield Network.

Like the CC, this model suggests that memories for concepts are activated based on the strength/weights of links between nodes. It is proposed that every node in the network is connected to every other node and it is only when the strength of the connections between nodes reaches some threshold that those nodes will become activated. Unlike the compound cue model, this includes both the activation and the suppression of nodes so that it is the overall pattern achieved and not simply the degree of activation of nodes that determines whether a concept is activated.

Masson suggests that there are two levels to the memory system, one is the 'perceptual' level which contains the visual pattern for word identification and the other is the 'concept' level which

includes the nodes which represent the concept itself. As such, when a word is identified visually, the perceptual network then activates the conceptual network so that the concept it represents becomes active. Priming occurs because the time taken to shift from a prime concept to a related target concept is shorter than the time taken to shift from a prime to an unrelated target as the related targets have a similar pattern of activation and so fewer changes are required.

1.2.2.6 Success of the Three Theories in Explaining Priming Results

1.2.2.6.1 Degree of Relatedness

The SAT suggests that there is a time period associated with the action of spreading activation within the network. Some have estimated this time at 100 or so milliseconds per node. Although no specific evidence for this decision is provided (Collins & Quillian, 1969). This suggestion has received criticism from both the CC and the DNM. The SAT suggests that activation spreads from the initially activated node, to the closely related nodes, then on to the less closely related nodes. As such, priming should be less and should take longer to occur for less closely related targets. Results of work by Ratcliff and McKoon (1981) demonstrated that while less closely related targets did demonstrate smaller degrees of priming, the onset of priming was not different between the two. In an updated version of SAT by Collins and Loftus (1975) it was suggested that instead of 100 milliseconds, travel time between nodes may be less than 10 milliseconds although they provide no evidence for this. The lack of difference in priming onset for closely versus distantly related pairs does not pose a problem for either the CC or the DNM. The CC does not assume any time period for a spread of activation as it assumes the prime and target access memory at the same time. The DNM proposes that changes from prime to target are as long as it takes for the network to shift to the target pattern.

1.2.2.6.2 Indirect Priming

So far, direct relationships between word pairs have been the focus of discussion i.e. CAT-DOG. Indirect pairs describe pairs that are related via their common association to a third word/concept. For example LION-STRIPES are related via their association with the word TIGER. Pairs of this type have also been found to elicit priming effects, although this effect is often smaller (explained further in section 4.4). This effect can be explained by the SAT which suggests the spread of activation decreases as it moves further from the prime. Ratcliff and McKoon (1988) deny that indirect priming has been proven to exist in their early article, and thus, do not attempt to account for it in their CC. In a later article they suggest that in fact, indirect priming does occur, and it occurs because the prime and indirect target are related, just not to the same degree as directly related pairs (McKoon & Ratcliff, 1992). This approach rejects the idea that mediation is necessary for a relationship between the prime and target to exist. The DNM can also account for this finding as indirectly related pairs share less of the same pattern than do directly related pairs but more of the pattern than do unrelated pairs (a mechanism similar to the CC).

1.2.2.6.3 Backwards Priming

Backwards priming describes the situation when the target is presented before the prime when pairs are related by association only, i.e. TRAFFIC-JAM. Intuitively, one might expect that there would be no priming effects if you swapped the order of the stimuli i.e. JAM-TRAFFIC. In actual fact, research has demonstrated that backwards priming does occur. The SAT does not offer any explanation for why backwards priming is able to occur but it would seem to fit without difficulty. This phenomenon poses no difficulty for the CC because when the stimuli are presented as a compound

cue, the order of cue presentation is irrelevant. Backwards priming can also be accounted for by the DNM as the time taken to shift pattern is unaffected by the order of primes and targets.

1.2.2.6.4 Intervening Word

Another problem with the SAT is that it does not account for the finding that an unrelated word put between a prime and target can eliminate priming. It is not clear how an unrelated word, which would be expected to activate some other part of the network, would interfere with two closely related words being activated near one another (Masson, 1991). Both the CC and the DNM can account for this finding. In the CC, an intervening word would decrease the familiarity of the compound eliminating priming. In the DNM it would increase the time taken to shift to the related target as the pattern would have to change to represent the unrelated word and then change again to match the related target. The finding that priming is eliminated in the presence of an unrelated word is not clear cut as some authors have found that priming can occur even when an intervening word is added (Plaut, 1995).

1.2.2.6.5 Ambiguous Word Pairs

Ambiguous word pairs describe those in which the prime has more than one meaning. For example, BANK has two possible meanings, one relating to money and the other to a river. Money is considered the dominant meaning of this term because it is what people generally think of first when they think about the word bank. Because RIVER is usually only considered after BANK, it is regarded as the subordinate meaning. Studies show that priming effects are equal for subordinate and dominant meanings of an ambiguous word in conditions that encourage automatic processing (i.e. quick and unconscious processing). When controlled processing occurs (i.e. strategic, conscious processing),

priming is generally only found for one meaning of the word (the dominant meaning if no further context is given). The DNM accounts for this finding by suggesting that although one perceptual pattern may represent an ambiguous prime; two different patterns may be connected to this representing the two possible word meanings. The SAT accounts for this by proposing that activation is only maintained for the more relevant option. The CC suggests that priming occurs as long as the ambiguous target is included in the compound and dictates that contextual information becomes included in the compound over time and, as a result, the initial ambiguous prime is pushed out so that only the relevant associations of the prime are maintained.

1.2.2.6.6 Expectancy Effects

If a participant is told that some targets will be related to primes, they might start expecting certain targets to appear i.e following the prime DOG, participants might guess that CAT will appear next. The SAT, in conjunction with Posner and Snyder's (1975) theory of attention, can explain the impact of expectancy effects. They suggest that when conditions are such that a participant may predict the target after presentation of the prime word, a set of possible outcomes are primed to be activated in preparation for the upcoming target. This theory can also explain inhibition which is associated with expectancy. When the participant has expected targets primed, the presentation of an unexpected target requires that the network abandon the expected set before it can activate the presented target. The time taken to do this leads to inhibition. Neither the CC nor the DNM are able to explain these expectancy effects.

It is clear that none of the theories discussed here is capable of explaining all the priming effects found in the literature. Instead, each offers a unique contribution to our understanding of these phenomena.

1.2.3 The Access/Storage Debate

Theories regarding the nature of the semantic deficit in schizophrenia are still scarce. The access versus storage debate has been adopted from dementia research as a possible framework for investigating the semantic deficits seen in schizophrenia. The results of investigations studying this dichotomy have provided support for both propositions (Allen & Frith, 1983; Aloia, Gourovitch, Weinberger, & Goldberg, 1996; Doughty, Done, Lawrence, Al-Mousawi, & Ashaye, 2008; Elvevag et al., 2002; Elvevag, Weinstock, Akil, Kleinman, & Goldberg, 2001; Laws, McKenna, & Kondel, 1998).

Warrington and Shallice (1975) offered four factors which would differentiate between an access or storage problem of semantic memory. These include attributes, consistency, frequency and cueing effects. Rossell and David added 'priming' to the list in a later publication (2006).

Table 1.4 *Access versus Storage Deficit in Semantic Memory*

Effect	Access Disorder	Storage Disorder
Category Level	*Attributes intact* Superordinate information equivalent to attribute information	*Attributes impaired* Superordinate information better preserved than attribute information
Consistency	*Inconsistent response* can sometimes retrieve a piece of information and sometimes not	*Consistent response* can always or never retrieve a piece of information
Cueing	*Cueing effect* helped by cues	*No cueing effect* not helped by cues
Frequency	*No frequency effect* same ability to name high and low frequency items as controls, with slight advantage for high frequency items	*Frequency effect present* considerable difficulty in naming low frequency items which appear to be 'lost' first
Priming	*Normal priming present* related pairs responded to quicker than unrelated	*Hyper-priming present* speed advantage to related pairs greater versus controls

Table 1.4 includes the criteria indicative of an access versus a storage problem and I will describe each criterion in more detail here:

'Category level' refers to the finding that when the semantic system degrades, the specific attributes that differentiate between members of a category break down while the more general descriptions remain intact. For example, consider the example of a peacock; a peacock is distinguished by its unique plumage. In a degraded system, knowledge of the plumage may breakdown while generic features of the category BIRD remain, for example, the knowledge that it has feathers and a beak. If the disorder is one of access however, the knowledge that a peacock has a unique plumage remains.

The consistency effect suggests that if a concept is intact, the participant's recognition of this item should be consistent in the face of a storage only problem. Meaning that, an item that is intact will be consistently recognised across tasks whilst a degraded item will be lost, regardless of the task. If it

is an access problem, the retrieval of the item may be inconsistent. That is, words may not be retrieved spontaneously but may be retrieved with the help of a cue (discussed next).

As indicated, if a cue improves performance, then the individual likely has an access deficit. Cueing provides an external support for accessing memory which compensates for access difficulties. A degraded store will not benefit from the addition of cues as the item is not available to be found in the semantic store.

A frequency effect describes a greater difficulty in naming low frequency versus high frequency words, this effect is indicative of a storage problem. No frequency effect would reflect an access problem. This is based on the proposition that a break down in the semantic store would result in the loss of less frequently used words first as their connections to other items are less and the pattern of activation is also less making them more vulnerable to breakdown. This is similar to the superordinate/subordinate distinction whereby features that are less established in the system break down earlier than well-established features.

Finally, with regards to semantic priming, if pairs included in the task are made up of pairs of words from the same category (ROBIN-PEACOCK; DOG-WOLF) then hyperpriming might occur (Rossell & David, 2006). The logic behind this assertion is that as the distinguishing features of the examples are lost, they will be regarded by their shared qualities making them more similar to one another. In extreme cases, ROBIN-PEACOCK might be broken down until they retain only the features that describe their shared superordinate category: BIRD-BIRD. This would facilitate recognition of the pair's relationship leading to hyperpriming. Indirect pairs (pairs connected via a

third concept: LION-STRIPES connected by TIGER) have not been investigated in relation to attribution breakdown. Following the same logic however, it might be expected that among those individuals demonstrating hyperpriming for category pairs, indirect pairs would not be regarded as related. If the concept of TIGER has lost its distinguishing features (the fact that it has stripes) then the concept of STRIPES will not be linked to TIGER so no priming between LION-STRIPES can occur. Similarly, hyperpriming might be seen on a task consisting of high frequency pairs whilst hypopriming might be evident in this group for low frequency pairs.

In order to test all these possibilities, Rossell and David (1999) compared a schizophrenia group across five semantic tasks including knowledge of single word meaning and category membership, and both explicit and implicit examinations of word associations. The results showed that generally, the schizophrenia group performed consistently, they were more affected by frequency effects (more difficulty with low frequency words) and demonstrated hyperpriming. This is more suggestive of a storage deficit than an access deficit. It is important, however, to add that there was some evidence (particularly for one participant) of an access problem in addition to this storage problem.

Another study (Al-Uzri, Laws, & Mortimer, 2004) has also examined the access/storage debate using multiple tasks across two occasions so that the criteria of cueing, attributes and consistency could all be examined. The results of this study were in support of an access disorder. The authors suggested that the relatively young age of their participants (mean age of 34.3 years) might have contributed to their participants access only profile as there is some research that suggests that as individuals with schizophrenia get older, they demonstrate a pattern of retrieval more indicative of a storage deficit (Kondel, Hirsch, & Laws, 2006). This may be a legitimate contribution to the results however, in the

Rossell and David study (2006) which found evidence for both access and store disorders; their participants group was of similar age with a mean of 36.6 years. There has further been a suggestion that length of illness might be a more important mediator of the semantic deficit seen (Chen, Chen, Chan, Lieh-Mak, & Lieh-Mak, 2000). The participants from Al-Uzri's study had an average length of illness of 11 years whilst the Rossell participant's length of illness was 13.6. This is also not a particularly big difference. The size of the participant group may also have contributed to Al-Uzri's findings as well as they had only twelve participants versus the twenty four included in Rossell's study.

Another study examined the consistency criteria in a group of elderly schizophrenia participants and compared their performance to Alzheimer's and elderly healthy controls (Kondel et al., 2006). The results suggested that the schizophrenia group demonstrated significant anomia (comparable to the Alzheimer's group) and further, they demonstrated a consistency effect suggestive of a storage deficit. While an interesting finding, this study examined only one criterion and thus these results must be interpreted with caution.

More recently Doughty et al. (2008) compared a schizophrenia group to an Alzheimer's group on two semantic batteries to compare the groups on the access/store criteria of consistency, frequency, cueing and attributes. The Alzheimer's group demonstrated a pattern of degraded store with demonstrated consistency effects, frequency effects, a failure of cueing and a breakdown in attributes. The schizophrenia group on the other hand, demonstrated an uneven profile of performance. While they did demonstrate a consistency effect (across only two tasks as they demonstrated ceiling effects on other tasks), there was no effect for frequency. They also demonstrated improvement in performance with cueing and poor performance on subordinate versus superordinate items. This profile

demonstrates support for aspects of both an access and a storage deficit. The authors found no demographic correlations with performance except that general scores on the general symptoms cluster from the Positive and Negative Symptoms Schedule correlated negatively with the second level of a sorting task. The implications of this finding are not clear.

There is a small literature examining the access and storage debate using verbal fluency tasks. In a fluency task, participants are asked to say as many words as they can think of in one minute starting with a specified letter (phonological fluency) or to list all the examples they can from a category, for example, animals or fruit (semantic fluency). Responses are recorded and the number of responses per 15 second intervals is noted. A number of performance factors are used to support either the access or disorganisation hypothesis of semantic deficit.

It is suggested that a difficulty in accessing verbal memory generally should affect responses to the phonological and semantic fluency task equally. A disorganisation of the semantic memory system specifically should affect semantic fluency more than phonological fluency (Rossell, Rabe-Hesketh, Shapleske, & David, 1999). The reason being that, theoretically, the phonological store is separate from semantic memory (Glosser, Grugan, & Friedman, 1997; Squire, Knowlton, & Musen, 1993). A majority of research comparing semantic to phonological output in schizophrenia indicates that semantic fluency is indeed more impaired (Bokat & Goldberg, 2003; Henry & Crawford, 2005). This finding suggests support for the impaired storage proposition.

Another method for examining the access/storage question using fluency tasks was addressed by Joyce, Collinson and Crichton (1996). These authors examined performance on the semantic

fluency task with and without cueing and found that the schizophrenia group had impaired overall performance and demonstrated greater benefit from cueing than did the healthy controls. The fact that the schizophrenia group gained more benefit from the cues suggests that these cues helped to overcome a difficulty in access. A deficit in storage would not be aided by cues because if the concepts were stored in a disorganised manner, cues would not necessarily be stored near the concepts that needed to be accessed. The results of this study therefore support the proposition of an access deficit in this group. It should be noted however, that the cueing effect was only at trend level and there was a possibility that this result was influenced by ceiling effects amongst the controls. Finally, the schizophrenia participants also demonstrated some storage deficits on the Boston Naming Task suggesting that the deficits of this group did not reflect a pure access deficit (Laws et al., 1998).

Allen (1993) and Aloia, Gourovitch, Weinberger and Goldberg (1996) found that in comparison to healthy controls, their schizophrenia groups demonstrated less grouping of similar concepts and produced more bizarre associations on the semantic fluency task. This result is also indicative of a disorganisation problem. If the semantic store was disorganised then bizarre associations might be expected to occur. In an organised system, similar concepts should occur together, a symptom of a disorganised store might well be reflected in groups of less similar concepts. The issue with these studies is that they have relied on only one task to draw conclusions from. The previous studies examined that relied on multiple tasks demonstrated that different tasks may be associated with different patterns of impairment; some reflecting an access problem and some reflecting a storage problem.

While the results of these investigations relying on the semantic fluency task are intriguing, relying on this task alone is problematic. There is evidence that the semantic fluency task is somewhat reliant on executive skills which may be confounding the task (Barrera, McKenna, & Berrios, 2005). In Chapter Six, the role of executive function in completion of the semantic fluency task is discussed in more detail.

This debate has also been investigated using non-verbal stimuli (Laws et al., 1998). A series of famous faces were presented to a schizophrenia group and they were rated on their ability to recognise the faces presented. The results indicated that this group of participants were heterogeneous in their deficit profiles. Some demonstrated an access deficit pattern, some a storage deficit pattern and some a combination of the two. In addition, the authors noted that those participants who were unable to name many famous faces (interpreted as having a smaller semantic store) also demonstrated consistency and did not benefit from cueing. Those who had a normal level of recall for the names of the famous faces (normal store size) did not demonstrate a consistent performance and a benefit from cueing. This was interpreted as evidence that the greater the naming deficit, the greater the likelihood that participants will demonstrate a storage deficit. This could also be interpreted as evidence that schizophrenia participants can demonstrate either a predominantly storage like or predominantly access like deficit. Worse naming may reflect a smaller, more degraded store. In which case it makes sense that responses would be consistent and cueing would be ineffective. A pattern of intact naming suggests that the store may be intact in which case the finding that access cues helped and responses were not consistent would be expected. While there is some evidence that suggests that schizophrenia is associated with a deficit in the recognition of familiar faces (Archer, Hay, & Young, 1992; Caharel et al., 2007), this

does not appear to be a confound in the task because there is also evidence that recognition for famous faces is intact in schizophrenia (Joshua & Rossell, 2009).

The results of all these studies are inconsistent. It is becoming more obvious that schizophrenia is not going to be found to fit either option neatly. It is interesting that some individual's with schizophrenia do fit one or the other explanation, but this is not always the case. Future research should focus on trying to link specific patterns of deficit to specific symptoms or demographic details more closely. This has certainly been touched on in multiple papers but little focused investigation has been conducted on this particular point. The differing patterns also suggest that group studies are probably inappropriate and series of individual profiles should be examined as a more informative alternative.

1.2.4 Implicit/Explicit Memory Access

One of the main aims of the current thesis is to improve our understanding of semantic dysfunction in schizophrenia. There are a number of aspects of semantic processing that have received little attention in this disorder including the distinction between implicit and explicit access. This distinction will be investigated in the current thesis. In particular, implicit and explicit access to semantic memory will be explored in Chapters Two, Three and Four. In preparation for reading those chapters, the following section will provide definitions of implicit and explicit memory, a brief review of literature supporting the distinction between these two types of memory, examples of implicit and explicit semantic tasks and a review of the schizophrenia literature incorporating the most commonly used examples of these tasks. Finally, methods for matching tasks across implicit and explicit memory are described.

1.2.4.1 General definitions of 'implicit' and 'explicit' memory

Defining the terms 'implicit' and 'explicit' is complex as there are numerous definitions described in the literature. For the purposes of this thesis, broad definitions will be provided in this section.

Schacter (1987, p. 501) defined implicit memory as the process by which "previous experiences facilitate performance on a task that does not require conscious or intentional recollection of those experiences". Explicit memory has been defined more simply as requiring intentional access, or as being declarative in nature (Buckner et al., 1995). The simplest defining difference between the two systems/processes is that implicit retrieval occurs outside of conscious awareness, whilst explicit retrieval requires conscious effort (Horan, Green, Knowlton, Wynn, & Mintz, 2008). For the purpose of this thesis, we followed the direction of Schacter et al. (1989) in preferring to distinguish explicit from implicit memory in terms of intentional vs. unintentional retrieval processes. This is preferable to determining the difference based on the presence or absence of conscious recollective experience because it is easier to justify the distinction for the former.

To provide some background, the performance differences between implicit and explicit memory have been demonstrated in numerous populations. Brain injury case studies have provided one method for examining the separable functions of implicit and explicit access to memory. One such case study examined a man with a right occipital lobe lesion (Gabrieli, Fleischman, Keane, Reminger, & Morrell, 1995). This case provided evidence for a dissociation between implicit and explicit memory access as he displayed normal explicit visual memory with specific impairments in implicit visual

memory performance. In contrast a study by Knowlton and colleagues (1992) with amnestic patients demonstrated normal word stem completion after being exposed to a list of words, i.e. implicit performance, but were impaired in recognising the words when asked explicitly to do so. Dissociation in implicit and explicit performance has also been found based on age. One study compared young adults (under 20) to older adults (over 68) (Gopie, Craik, & Hasher, 2011), and found that older participants maintain their implicit memory abilities but demonstrated a decline in explicit memory when compared to the younger group. Another study (Naito, 1990), found that young children (aged 7) demonstrated similar implicit memory abilities to those of 12 year old children and adults. These older groups, however, demonstrated greater explicit memory abilities. Finally, some studies have found differences in implicit and explicit memory as a result of the effects of Diazepam (an anxiolytic) (Danion, Zimmermann, Willard-Schroeder, Grangé, & Singer, 1989). This study found that implicit and explicit access to episodic memory was differently affected with Diazepam impairing explicit memory access whilst sparing implicit access.

There are three possible explanations for why differences in access exist between implicit and explicit memory (Gabrieli et al., 1995): (1) Implicit and explicit memory belong to a unitary memory system in which implicit access is less demanding than explicit. In this case, implicit memory can remain intact in the face of impaired explicit memory because it is easier to access. (2) Implicit memory is a subsystem of a larger memory system devoted predominantly to explicit memory. In this case, damage to any part of the system is likely to impair explicit memory whilst implicit memory may remain intact. (3) Finally, implicit and explicit memory systems are totally independent. There is substantial support for the third option, with a large number of studies, including those mentioned, which report double dissociations. That is, some lesions can lead to impairments in explicit but not

implicit memory (this sits well with all three propositions) but also, they provide evidence for the opposite pattern. That is, a lesion may be associated with impaired implicit but intact explicit function (supporting only the third proposition) (Gabrieli et al., 1995; Keane, Clarke, & Corkin, 1992; Vicari, 2001).

1.2.4.2 Implicit and explicit semantic access in the literature

Dissociations in performance between implicit and explicit episodic memory are well represented in the literature (Gabrieli et al., 1995; Gopie et al., 2011; Knowlton et al., 1992; Naito, 1990). There is less information available regarding implicit and explicit function in semantic memory (Danion et al., 1989; Rogers & Friedman, 2008). The study by Danion et al. found that implicit and explicit semantic access was differently affected by diazepam (an anxioltyic), with this drug impairing explicit but not implicit memory. This suggests some dissociation in implicit and explicit access to semantic memory. Further, studies of implicit and explicit semantic access in Alzheimer's disease have found poor explicit semantic access, and reduced but less impaired implicit access (Rogers & Friedman, 2008).

In psychosis research, there has been significant investigation of the implicit/explicit memory divide with regard to episodic memory. This research suggests that in schizophrenia, explicit episodic retrieval is impaired while implicit retrieval is intact (Bazin & Perruchet, 1996; Clare, McKenna, Mortimer, & Baddeley, 1993; Sponheim, Steele, & McGuire, 2004). Despite the knowledge that semantic memory is impaired in schizophrenia, and that implicit and explicit semantic access can be differentially impaired in other conditions, very little research has been conducted to investigate these different access routes separately for semantic memory in schizophrenia. After a description of the

commonly used measures of semantic memory access, the schizophrenia literature in this area will be reviewed.

1.2.4.3. Explicit Semantic Memory Tasks

Explicit semantic tasks describe any memory task in which participants are informed that they are assessing the relatedness of pairs. In the current thesis, the 'explicit' task used has the instruction to search for relationships between two stimuli (a prime and a target). The participants are also given ample time to respond to pairs (further methodological details are provided in Chapter Three).

There are numerous aphasia and dementia tests, and test batteries that have been applied to schizophrenia in the investigation of explicit semantic memory deficits. The following is designed to take the reader through the logic behind the implicit and explicit tasks employed in this thesis. I will begin by describing a number of popular explicit and implicit task options. I will then review the literature regarding these various options. This is concluded with a discussion regarding the final task choices.

1.2.4.3.1 Western Aphasia Battery (Kertesz, 1979)

As the name suggests, this battery was designed as a measure of aphasia. It consists of eight subtests: (1) Content, (2) Fluency, (3) Auditory Comprehension, (4) Repetition, (5) Naming, (6) Reading, (7) Writing and (8) Calculation. Some subtests from this battery can be used as measures of semantic function. The fluency tasks assess spontaneous semantic output; the comprehension task can determine whether concepts from memory are intact, as can naming.

1.2.4.3.2 Hodges Semantic Memory Test Battery (Hodges et al., 1992)

The authors of this battery used 48 items across eight different tasks so that the integrity of items across tasks can be assessed. The tasks, adapted from other language batteries, include: (1) Fluency, (2) Naming, (3) Sorting, (4) Picture matching and (5) Generation of verbal definitions.

1.2.4.3.3 Peabody Picture Vocabulary Test (Dunn & Dunn, 1981)

The Peabody is a stand-alone measure of semantic memory. Participants are shown four items on a card, the examiner names one of the four items and the participant must correctly match the spoken name to the drawing of the item. The frequency of the items goes from high (dog) to low (abacus) over the 175 items included in the task. The original purpose of the Peabody was to assess auditory comprehension in children. As a naming task however, it can also provide a measure of semantic memory.

1.2.4.3.4 Pyramids and Palm Trees (Howard & Patterson, 1992)

The purpose of this test is to assess an individual's semantic access using words and pictures. Triads of items are presented with one item, the target, placed above two others. The target item must be compared to the two options below and the participant must determine which of the two options matches the target above. For example, if a pyramid is the target and the two options below consist of a pine tree and a palm tree, the person must make the link between the pyramid and the palm tree. There is another test based on this known as the Camel and Cactus test (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000). This task provides four options to choose from rather than two to increase the difficulty of the task.

1.2.4.3.5 Boston Naming Task (Kaplan, Goodglass, & Weintraub, 1983)

This task consists of 60 line drawings of objects ranging from high frequency items like a 'tree' to low frequency items like an 'abacus'. Participants are asked to name the objects and if they cannot, they can be given two clues, one phonemic and one stimulus cue.

1.2.4.4 Implicit Semantic Memory Tasks

There are a number of different implicit memory task formats. The main tasks used in the literature are word stem completion, word/picture fragmentation and priming. Only priming is discussed here as word stem completion and fragmentation tasks are measures of implicit learning as opposed to existing memories.

1.2.4.4.1 Repetition Priming

Repetition priming occurs when there is a faster reaction time to words or pairs of words that have been seen previously (Gras-Vincendon et al., 1994). This task would not be appropriate in the current thesis as it does not assess semantic function.

1.2.4.4.2 Masked Priming

Masked priming describes the process by which a prime is presented for a very brief period (somewhere between 10-40msec), and a pattern (usually a number of hash marks or asterisks) is presented before or after the prime or before and after the target (Angwin et al., 2004; Baving, Wagner, Cohen, & Rockstroh, 2001; Brown & Hagoort, 1993; Grossi, 2006). This type of task can be considered implicit because masking means that the participants do not recall seeing the prime, but

demonstrate that they have processed it by exhibiting priming effects. Further, because the prime is not 'seen' this prevents the development of expectancy and post lexical processing (Neely, 1989). Psychotic illness is associated with reduced perceptual abilities and a slowing of perceptual processing (Moritz, Ruff, et al., 2001). Despite these difficulties, masked priming has been used successfully in this group (Dehaene et al., 2003; Moritz, Ruff, et al., 2001). It has also been used successfully in analogue studies of psychosis. One study used the analogue of examining the effects of levodopa on healthy individuals (Angwin et al., 2004). These authors found that excessive dopamine lead to abnormal priming effects in healthy participants modelling psychotic symptoms.

1.2.4.4.3 Semantic priming

In semantic priming tasks, participants are presented with a series of pairs. Some of the pairs are semantically related (CAT-DOG), some of the pairs are unrelated (CAT-WINDOW) and some of the pairs contain a real prime and a non-word target (CAT-POING) (further details regarding the semantic priming task are covered in section 1.4 of Chapter One). There are a number of design manipulations which will increase the likelihood that semantic access during the priming task is implicit. One way is to provide a distractor task. For example, in the current thesis for the implicit priming tasks, participants are told to ignore the first word of the pair, and instead are asked to dedicate their time to determining whether the second word of each pair is a real or made up word, i.e. a lexical decision task. Another method is to provide a limited processing time for response. This method is supposed to prevent participants from noticing that some word pairs are in fact related. This was also considered in this thesis with only short processing times provided to participants.

1.2.4.5 Explicit Semantic Performance in Schizophrenia

As noted previously, explicit semantic function has been investigated using language tasks originally designed for use with aphasia or dementia populations. As such, they are not always sensitive to the semantic deficits found in schizophrenia. The following is a brief review of explicit semantic performance in schizophrenia focusing on those tasks most frequently used in this population.

Beginning with studies that have employed the Pyramids and Palm Trees task (P&P), Whittaker et al. (2001) found that their schizophrenia group performed at ceiling on this task and concluded that either: (1) the task was not difficult enough to detect the schizophrenia deficit and/or (2) the presence of the stimulus in front of the participants provides cues eliminating the effects of any access deficits that might usually impair performance. Their controls and schizophrenia participants were well matched for age (schizophrenia: 36.2 years, controls: 36 years). The schizophrenia group were also matched to controls on the NART and had an average length of illness of 15 years. More recently, Ragland et al. (2003) and Moelter et al. (2005) also found intact performance on this task. Ragland's study included 30 schizophrenia and 30 controls. The IQ of the schizophrenia participants was intact (NART = 98.2) and their age (33.92) was matched to controls (30.79) with an average length of illness of 10.24 years. Finally, Moelter's study included 17 schizophrenia and 17 controls matched for age (schizophrenia: 34.29, controls: 30.80). The schizophrenia group had intact premorbid IQ (NART=101.6) and length of illness was 10.51 years.

Intact P&P performance has not always been reported, with a number of studies finding impairments on this task (Bonner-Jackson & Barch, 2011; Gabrovska, Laws, Sinclair, & McKenna, 2003; Vogel et al., 2009). Vogel found that this impairment was actually only at trend level (p=0.051),

and the only demographic information available about the participants was their length of illness (8.42 years) with a NART score of 82.42. Bonner-Jackson et al. (2011) included 23 schizophrenia (aged 36.6) and 24 controls (aged 37), and found a significant difference in group performance. Intelligence estimates were not calculated but the schizophrenia group did perform more poorly than controls on the vocabulary and reasoning subscales from the WAIS (oddly, there was no group difference in performance on the Similarities subscale, a semantic measure). Gabrovska et al. (2003) found that even in schizophrenia participants with intact full scale IQ functioning on this task can be impaired with authors suggesting that visual form impairment may contribute to these results.

A number of case study papers have utilised the P&P (Laws, Kondel, & McKenna, 1999). In one of his studies (Laws, McKenna, & McCarthy, 1996), Laws found that of 10 case studies, two participants were significantly impaired on the task. Laws and colleagues (1999) examined one participant (TC) with severe thought disorder on a range of semantic tests. They found that TC's performance on the task was only at chance level. Another case study (DH) displayed a severe deficit on this task, also with performance at chance level (Laws, Leeson, & McKenna, 2006). These studies cannot be relied upon to suggest that schizophrenia generally is associated with a deficit on this task because the authors have often selected these participants based on their poor overall semantic function.

There is a similar but more difficult version of the P&P, known as the Camels and Cactus test (Bozeat, Lambon, Patterson, Garrard, & Hodges, 2000). This task presents one stimulus at the top of the page and provides four stimuli to choose between rather than the two stimuli included in the P&P. The added difficulty of this task makes it appealing to use with schizophrenia groups as it may provide

a more sensitive measure of the semantic deficits in seen in this group. In one study which utilised this task, a group of schizophrenia participants were found to perform normally if levels of thought disorder were low but more poorly if they had high levels of this symptom (Barrera et al., 2005). Another study found deficits in their schizophrenia group regardless of their symptom profiles (Doughty, Done, Lawrence, Al-Mousawi, & Ashaye, 2008).

In sum, three studies suggest intact performance in schizophrenia on the P&P. The results of another study are not clear. Two further investigations indicate impairment; and a series of case studies provide evidence that poor semantic function is predictive of poor performance on this task. As is often the case with schizophrenia research, it is difficult to determine which factors are responsible for differences between studies. It appears, from those studies reporting impaired performance that overall IQ is not the determining factor as some groups were low and others intact. Neither age nor length of illness appears to explain the results and there was not enough information regarding medication or symptom profiles to examine their contribution to the results.

Another well-known explicit measure of semantic function is the Boston Naming Task (BNT), described above (Kaplan et al., 1983). There is some evidence that schizophrenia performance declines with age (Goldberg, Hyde, Kleinman, & Weinberger, 1993), a finding that has been confirmed by later research (Hyde et al., 1994). As such, in the review of the papers using this task, the age of the participants is considered.

There is some research which finds no schizophrenia deficit on the BNT (Gold, Randolph, Carpenter, Goldberg, & Weinberger, 1992; Goldberg et al., 1998). The study by Gold et al. (1992)

included 36 schizophrenia participants (33 years) and 18 controls (33.5 years). The groups were matched across demographic variables apart from full scale IQ which was not available for controls. The authors found no difference between the groups in BNT performance. Goldberg et al. (1998) compared 23 schizophrenia participants (35 years) to 23 healthy controls (also 35 years), and found no schizophrenia deficit on the BNT; not even amongst those participants with high levels of thought disorder (no other symptom information was provided). These two studies included participant groups well matched on age.

There is also evidence for a deficit on the BNT (Gourovitch et al., 1996; Joyce et al., 1996). Joyce et al (1996) compared 50 schizophrenia participants (mean age 36.6 years) compared to 25 controls (mean age 33.56 years) on the BNT, and found that their schizophrenia group were impaired in spontaneous naming and remained impaired even with the assistance of cues. The authors noted that BNT performance did not correlate with any of the symptom or demographic variables collected. Another study (Gourovitch et al., 1996) also found a significant difference between the schizophrenia and control group. There were 27 participants in the schizophrenia group (average age 38.74) and 22 healthy controls (average age 33.04). There was no other symptom or demographic information provided. While the ages of the schizophrenia groups appear older than the controls, there were no significant age differences between these groups in either study. Therefore, it is unlikely that age is responsible for the performance differences found between studies. There is not enough comparable symptom data, medication data or illness history data to determine whether these variables might be contributing to differences in study results.

1.2.4.6 Implicit Semantic Performance in Schizophrenia

In terms of implicit semantic processing, there is a large body of literature examining semantic priming effects, with such tasks often referred to as implicit (Clare et al., 1993; Kreher, Goff, & Kuperberg, 2009; Kuperberg, Lakshmanan, Greve, & West, 2008; Neill et al., 2011; Rissman, Eliassen, & Blumstein, 2003; Rogers & Friedman, 2008). The results of these semantic priming studies are inconsistent when directly related pairs are considered (LION-TIGER), but there appears to be some consensus with regards to indirectly pairs (LION-STRIPES), with abnormal schizophrenia performance reported (Rossell & Stefanovic, 2007). This literature is examined in greater detail in Chapters Two, Three and Four.

One EEG study has created their own implicit and explicit semantic tasks to compare access to the semantic system in schizophrenia (Kreher, Goff, & Kuperberg, 2009). The implicit task required participants to view word pairs (some unrelated, some directly related, some indirectly related) with the instruction to press a button in response to any food words as the distractor task (task SOA was 350msec). The explicit task included the same SOA but instructed participants to press a button to indicate whether word pairs were unrelated, directly related or indirectly related. Eighteen schizophrenia and eighteen matched controls were included. Length of illness for the schizophrenia group was 17 years with a PANSS total of 57. The results showed that in response to the explicit task, there was a reduction in the N400 effect whilst implicit performance was normal with intact N400, or in the case of thought disordered participants, an increased N400 effect. This result was true for both direct and indirectly related pairs. These authors did not examine RT behavioural data but found no group differences on behavioural error results. In summary, the only study in the literature to have

compared implicit and explicit access suggests impaired explicit but preserved implicit performance (not including thought disordered performance).

There is one schizophrenia study that examined indirect pairs specifically on an explicit task. The task from this study has in fact been adopted for the current thesis (Assaf et al., 2006). Assaf and colleagues examined explicit indirect priming in a group of 16 schizophrenia and two schizoaffective participants (age 38.6, normal NART, illness duration 17.7 years) compared to 16 matched controls using MRI. Prime and target were presented for 2.7 seconds with a 5.5 second gap between pairs. The behavioural results showed that the schizophrenia group tended to make more false positive responses, that is, they falsely categorised unrelated pairs as related. They were also slower to correctly recognise pairs as related.

1.2.4.7 Matching implicit and explicit tasks on reliability

Some authors have argued that differences in implicit and explicit performance may actually reflect differences in task reliability rather than the function of two separate memory systems (Buchner & Wippich, 2000). These authors specifically proposed that implicit tasks are generally less reliable than explicit tasks. Explicit tasks often provide strict structure (through instruction) and a yes/no or old/new response (limiting response options thereby reducing variability), whilst implicit tasks, like word stem completion, are less rigid in their instruction providing more room for interpretation and a greater variability in responses. This greater variability can lead to more 'noisy' and less reliable data. It is generally found that more reliable tasks will demonstrate true differences between groups whereas less reliable data might mask differences in their greater response variability. Therefore, some studies comparing groups and finding impaired explicit and intact implicit memory may be reflecting

methodological problems as opposed to real differences in implicit and explicit processing. The likelihood of this occurring is dramatically reduced when implicit tasks are well matched to explicit ones. For example, using a priming task in which participants must provide a yes/no response and have a limited time for response.

1.2.4.8 Implications for Task Choice for the Current Thesis

The preceding information provides guidance in task choice for the current thesis. The literature clearly indicates that semantic priming is the most appropriate implicit task choice for the following reasons: (1) There is some degree of consistency in the schizophrenia literature indicating that, when indirect pairs are used, there is a schizophrenia specific performance pattern (see Chapters Two, Three and Four for further discussion about indirect priming in schizophrenia). (2) This task can be well matched to explicit semantic tasks based on the constraints of priming (limited response options).

In contrast, the literature on direct implicit performance in schizophrenia is mixed (Chenery, Copland, McGrath, & Savage, 2004; Quelen, Grainger, & Raymondet, 2005; Rossell & David, 2000), with some evidence for reduced, some for normal and some for increased priming. Despite this confusion in the literature, a direct implicit task will also be included in the semantic test battery used for this thesis. The purpose being that it will help to provide a fuller picture of semantic functioning in a single participant group.

To compare implicit and explicit semantic function, it is beneficial to match the implicit tasks to the explicit tasks where possible. Therefore, the decision to rely on a semantic priming task as the

implicit task placed considerable constraints on the choice of explicit priming tasks. As I've noted, the schizophrenia literature has suggested that implicit priming tasks utilising indirect relationships elicit the most consistent findings. Therefore, we wished to include both a task that measured direct relationships and another that examined indirect relationships. Traditional explicit semantic tasks do not include indirect conditions. This meant it was not possible to use existing test batteries. Further, they do not address the hypotheses under study in this thesis. See Appendix A for an examination of all possible tasks.

It was determined that, for the indirect explicit task, the Object task created by Kraut (Kraut, Kremen, et al., 2002) for use in a healthy population and employed by Assaf (Assaf et al., 2006) to examine schizophrenia performance would be used. This task requires participants to examine two words (similar to the implicit priming format) and determine whether the pairs were indirectly related. It also provides information about schizophrenia performance to guide hypothesis generation. A direct version of this task was created (known from here on as the Association task). This task had exactly the same format as the Object task but included direct instead of indirectly related pairs.

The limitations of my task choices are that different stimuli are included in the implicit and explicit tasks. A large number of stimuli were required in the implicit task and including those stimuli in an explicit task would have made it too long. The ideal task design would have included the same stimuli across the implicit and explicit tasks. This would have (1) made the tasks more comparable and (2) allowed for an in-depth examination of the access/storage debate.

Therefore, for this thesis, semantic function will be examined using (1) a direct implicit priming task (2) an indirect implicit priming task (3) a direct explicit task (the Association task) and finally (4) an indirect explicit task (The Object task).

1.3. Symptoms of Schizophrenia

1.3.1 Formal Thought Disorder (FTD)

Thought disorder (TD), a term often used synonymously with the term "disorganised language" (Andreasen, 1979), is a symptom commonly experienced by individuals with schizophrenia. Kraepelin (1913) gave one of the early and most detailed accounts of TD describing it as the "incoherence of thought". One problem with defining and conceptualising TD is that there is a general lack of agreement as to the meaning of terms used to describe it (Andreasen, 1979). For this thesis, the "Thought, Language and Communication Scale" (TLC) by Andreasen (1979) is used as a guide to define and characterise the various symptoms of TD. The term TD is used loosely and can sometimes be used to describe disordered thought content including delusions and auditory hallucinations (Simpson & Davis, 1985). As a part of Andreasen's attempt to tighten up this concept, the word 'Formal' in front to signify that it referred to evidence of language and communication abnormalities (Andreasen, 1979). Since its creation, the TLC scale is widely accepted and has been employed in a majority of studies examining TD (McKenna & Oh, 2005). Andreasen defined 18 examples of thought disorder. Each of which is described here.

1. *Poverty of speech:* Defined by a restriction in spontaneous conversation. Individuals with this symptom generally provide necessary information without elaboration. Their answers are brief and concrete.

2. *Poverty of content of speech:* Noted when the individual produces a normal amount of speech but this speech conveys very little information. So language tends to be vague and over abstract.
3. *Pressure of speech:* This is defined by a marked increase in the amount and speed of speech. The individual is also often loud and difficult to interrupt.
4. *Distractible speech:* Occurs when an individual is easily distracted by objects or noises in their environment. They might stop in mid-sentence to comment on something nearby.
5. *Tangential speech:* Defined by digressive responses that may be of superficial relevance, if any relevance at all can be detected.
6. *Derailment:* Similar to tangential speech but instead of offering a digressive response immediately, the individual will initially begin answering the question but will drift away or suddenly change the course of their answer.
7. *Incoherence:* When the individual simply cannot be understood. Often characterised by disturbances at the sentence level rather than drifting or irrelevant answers.
8. *Illogicality:* Occurs when an illogical conclusion is drawn. For example, “women have children. You are a woman so you must be a mother.”
9. *Clanging:* When word sounds rather than meaning determine the individual’s speech. Often using words together because they rhyme or create a pun.
10. *Neologisms:* The creation of new words that do not mean anything to anyone but the individual who invented them.
11. *Word approximations:* Can take the form of describing the object rather than using its name. For example, a watch is a “time vessel”.

12. *Circumstantiality:* Similar in some ways to tangentiality and derailment. Different in that the individual speaks about a topic without providing the desired answer rather than jumping onto or drifting off onto a totally different topic.
13. *Loss of goal:* Often occurs with derailment when the person drifts off a topic. Different from circumstantiality because the person never returns to the topic.
14. *Perservation:* The repetition of words or ideas.
15. *Echolalia:* Occurs when the individual imitates what others say; like a parrot.
16. *Blocking:* When an individual suddenly stops mid sentence and spontaneously reports that they cannot remember what they were trying to say.
17. *Stilted speech:* When speech is stilted or excessively formal.
18. *Self reference:* Brings all conversation back to themselves.

An important note by Andreasen is that FTD is not a unitary concept and it is useful to discuss it in terms of 'positive' and 'negative' thought disorder. Positive FTD refers to an excess of speech, for example pressured speech, whereas negative FTD refers to a decrease in speech, e.g. poverty of speech. Positive FTD is more often associated with acute schizophrenia and negative FTD with chronic schizophrenia (McKenna & Oh, 2005). The distinction between positive and negative thought disorder is an important one and is particularly relevant to study one of this thesis (Goldberg et al., 1998). This is because research indicates that people with positive versus negative FTD respond differently to cognitive tasks (Maher, Manschreck, Redmond, & Beaudette, 1996; Moritz, Mersmann, Kloss, Jacobsen, Wilke, et al., 2001).

FTD is not unique to schizophrenia and has been noted in individuals with mania (who often exhibit positive FTD) and depression (more often negative FTD) and in healthy individuals who are highly creative (McKenna & Oh, 2005). It can also be elicited in people when they are very tired (Andreasen, 1979). Bleuler (1911) asserted that FTD was pathognomic of schizophrenia; but, it is now generally accepted that not all individuals with schizophrenia will display this symptom, and it is not a constant amongst those individuals who do experience it (Andreasen, 1979).

1.3.2 Formal Thought Disorder and the Semantic Network

The link between a semantic memory deficit and FTD was developed based on the observation that participants with the symptom of FTD appeared to have a greater abnormality in their semantic memory store than did those participants with schizophrenia without the symptom of FTD (Maher, 1983). In their investigation of the attentional capacity of individuals with FTD, Maher and colleagues suspected that the semantic network of individuals with FTD might be overactive. They suggested that this might lead to a difficulty in focusing attention on relevant stimuli which would then lead to intrusions in speech. This "activated association's hypothesis" was taken further by Manfred Spitzer and his laboratory. They explored this phenomena and found that participants with FTD exhibited enhanced semantic priming compared to controls (Spitzer, Braun, Hermle, & Maier, 1993).

This finding was interpreted as evidence that the spread of activation in the semantic network was greater amongst those individuals with FTD. Alternatively, it was also hypothesised that such a finding might reflect the failure of some normal inhibitory process within the network. These studies are explored next.

1.3.3 Formal Thought Disorder and Semantic Priming Studies

Kerns and Berenbaum (2002) conducted a meta-analysis to examine priming results in FTD. They focused on studies published between 1990 and 2000 and found eight relevant articles. Of these eight articles, three reported finding hyperpriming and five found hypopriming. On close examination, the authors found that in the three studies that reported hyperpriming, the relatedness proportion and the non-word ratios were high, a combination of factors thought to lead to semantic matching, a postlexical process (described in section 4.3). The authors concluded that semantic matching was the cause of hyperpriming in FTD.

A more recent review of the literature on semantic priming tasks in schizophrenia (Rossell & Stefanovic, 2007) has highlighted the degree of heterogeneity in results. The authors suggested a number of experimental variables that may have impacted on the outcomes of these studies. These include the type of priming task employed, the length of the SOA, the ratio of the different pair types included, the nature of the relationship between the word pairs, whether word pairs were presented unilaterally or bilaterally, and the medication and illness characteristics of the participants. The importance of these factors has been discussed previously; here the variance of results that can occur as a result of these factors will be investigated. The review will be limited to those articles that have taken FTD into account. It is relevant to point out that a majority of the research is in agreement with the finding that individuals with schizophrenia demonstrate reduced priming when controlled processes are examined and the inconsistency is noted amongst studies examining automatic processes (Minzenberg et al., 2002). Because so few articles have examined the role of FTD in priming, each paper will be examined separately and they will be organised by priming results obtained.

1.3.3.1 Review of the Literature Finding Hyperpriming in FTD

Eight studies in this review found hyperpriming. Each of these studies will be discussed in turn. Table 1.5 summarises the findings of these studies.

Study 1: An early investigation by Manschreck et al. (1988) compared individuals with schizophrenia with and without FTD (12 with and 9 without) to those with unipolar affective disorder (9) and healthy controls (11) on semantic priming using a lexical decision task. FTD was rated using the Schedule for Affective Disorders and Schizophrenia (SADS). An individual with ratings above three or more on any FTD related item was classed as thought disordered. Word pairs used in this experiment were related by association and the stimulus onset asynchrony (SOA) was 250 msec. The ratio of words to non-words was 40% words to 60% non-words and the relatedness proportion was 20%. The two schizophrenia groups were matched for medication dosage. The results revealed significantly more facilitation for pairs related by association than the unrelated pairs across groups. This effect was significantly greater amongst the FTD group.

Study 2: Spitzer, et al. (1993) used a lexical decision task to examine both automatic and controlled processing. The authors employed both direct and indirect pairs; and compared the performances of both a FTD and non FTD schizophrenia group to healthy controls. To encourage automatic processing, an SOA of 200ms was used; the prime was presented for 200ms. The controlled processing condition consisted of an SOA of 700ms (200msec prime presentation and 500msec interstimulus interval). Fifty individuals with schizophrenia (twenty one with FTD, twenty nine without) and fifty normal controls were included in this study. It is unknown whether the clinical

groups were matched for medication. The schizophrenia group was split based on a single item of the Brief Psychiatric Rating Scale (BPRS) known as 'conceptual disorganisation' which reflects 'general FTD'. The ratio of words to non-words was 50% each and relatedness proportion was 33%. The results for the direct condition were the same for both automatic and controlled processing and showed that the FTD group exhibited greater priming than both the controls and the non-FTD schizophrenia group. For indirect priming at the automatic level, neither the controls nor the non-FTD group demonstrated priming. The FTD group on the other hand demonstrated significant priming effects. At the controlled level however, all three groups demonstrated significant priming effects. Authors concluded that the FTD groups increased priming was consistent with the theory of increased activation or decreased inhibition.

Study 3: Moritz et al. (2001) also examined priming in FTD using indirect priming pairs and a lexical decision task. FTD was rated using the Positive and Negative and Disorganised Syndrome Scale (PANADSS). Participants were divided into a FTD and non-FTD schizophrenia group based on their rating on one item of this scale. This was the 'loosening of association' item. This item captures some but not all symptoms of FTD. Forty four individuals with schizophrenia were included, sixteen with FTD and twenty eight without. Thirty healthy controls were also included. Schizophrenia participants were matched for medication dosage. The relatedness proportion was 50% and the SOA used was 200ms. The schizophrenia group but not the control group demonstrated enhanced priming in both the direct and indirect condition. When the schizophrenia group was split into FTD and non-FTD, the significance remained only for the FTD group and the degree of priming for this group was significantly greater than that found for the control group.

Study 4: This study relied on a word pronunciation task to examine semantic priming in FTD (Moritz, Mersmann, Kloss, Jacobsen, Andresen, et al., 2001). Once again, FTD was rated using the 'loosening of associations' item from the PANADSS. Fifteen FTD and thirty non-FTD individuals participated. Thirty healthy controls were included. Non-words are not included in pronunciation tasks. The relatedness proportion was 55%. Medication was not reported. A number of different word pair relationships were included in the stimuli. Some targets reflected the dominant meaning of a prime and others the subordinate meaning. Some pairs rhymed, others were semantically related and some had no relationship. Automatic processing alone was examined using an SOA of 200ms; this was also the prime presentation time. Results showed that there were no significant differences between the groups in degree of priming to rhyming pairs or dominantly related pairs. Interestingly, the FTD group were faster than the other groups in reacting to the subordinate word pairs. This finding was seen to support the increase activation/ decrease inhibition theory as less closely related words were quickly accessible.

Study 5: Moritz, Woodward, Kuppers, Lausen and Schickel (2002) in a more recent study once again used a pronunciation semantic priming task to examine FTD. This study extended the previous one as it included indirectly related pairs in the stimulus set. It also included two baselines, neutral and unrelated, to ensure the priming effects were not being perceived as a result of an inappropriate baseline. The 'loosening of associations' item from the PANADSS was used to rate FTD. Medication was reported for the clinical group as a whole but not when split into two groups. Twelve participants with schizophrenia had FTD and twenty without. Sixty five healthy controls were included for comparison. An SOA of 200ms was used and the relatedness proportion was 50%. It was unclear whether participants were matched on this variable or on medication once the clinical group was split.

Results showed that when the unrelated pairs were used as a baseline, there were no significant group differences. When the neutral baseline was used, the FTD group demonstrated a significantly greater degree of priming. For the indirect condition, the FTD group demonstrated significantly more priming than did the other two groups. This result was also seen as evidence for increased spread of activation amongst FTD individuals.

Study 6: Chenery, Copland, McGrath and Savage (2004) created two stimulus lists one with a low proportion of related pairs (33%), and 25% non-word pairs; presented at a short SOA (250ms). The other list included a high relatedness proportion (75%) and 67% non-word pairs, presented at a long SOA (2000ms). This was to enable an examination of automatic and controlled processes in priming. Both close and distant association relationships were examined. The authors employed a novel version of the lexical decision task. Instead of a word pair being used in each trial, three words would appear one after the other. These included two primes and a target. This allowed for an examination of the influence of context on performance as sometimes one or both primes were related to the target. Fourteen individuals with schizophrenia and twelve healthy controls were included. The TLC was used to rate FTD and overall score was based on four of the items assessing positive FTD symptoms. They found that higher ratings of FTD correlated with increased priming at a short SOA, particularly for distantly related associates. It was also found that the schizophrenia group demonstrated faster RT in the low relatedness condition, opposite to that of controls. This was interpreted as a deficit in updating context. Priming was absent for all participants with schizophrenia at a long SOA.

Study 7: Quelen, Grainger and Raymondet (2005) also used a three word priming experiment however, their technique differed. Participants saw a prime and then a briefly presented, pattern-masked target (target flash duration corresponds to a pre-determined perceptual threshold for each participant). They were then shown two words on the screen at once. One was the briefly displayed target and one was a foil. The participants had to determine which of the two the target was. Four conditions were used in this paradigm 1) neither the target nor the foil were related to the prime 2) both the target and the foil were related to the prime 3) only the target was related to the prime 4) only the foil was related to the prime. The type of relation between pairs was not specified. Twenty individuals with schizophrenia and twenty healthy controls participated. The TLC was once again used to rate FTD. Primes were presented for 500ms and the length of time needed to perceive the prime was calculated separately for each participant to suit their perceptual requirements. Relatedness proportion was not reported. Results revealed that participants with schizophrenia did need more time to perceive stimuli. Similar degrees and patterns of priming were found when the schizophrenia and control group were compared. It was found that there was a significant correlation between the symptom of FTD and enhanced priming effects.

Study 8: More recently, Lecardeur et al. (2007) has attempted to understand the separate roles of facilitation (automatic processes) and inhibition (controlled processes) in FTD. Fifteen individuals with schizophrenia and FTD and fifteen healthy controls participated in this study. FTD was measured using the TLC and only low levels of FTD were detected. Both automatic and controlled processing was examined using a lexical decision task. In the automatic condition, a low relatedness proportion of 10% was used and the SOA was 250ms. In the controlled condition, the relatedness proportion was increased to 30% and the SOA was 500ms. The non-word ratio was kept at 50% for both tasks. The

length of prime presentation was not reported. Word pairs were related semantically (BIRD-ROBIN) or by attributes (ZEBRA-STRIPES). Despite evidence suggesting that inhibitory processes do not occur at an automatic level, both a neutral and unrelated baseline was included at both SOAs. This was necessary to examine whether an increase in facilitation or an increase in inhibition was responsible for the finding of enhanced priming amongst FTD individuals. Results of this study revealed that both groups demonstrated priming under both conditions but the FTD group exhibited enhanced priming in both conditions. A closer examination revealed that this enhanced priming was the result of increased inhibition in reaction to unrelated words for this group. Although steps were taken to reduce controlled factors in the automatic condition, the appearance of inhibition in that condition would suggest that semantic matching (discussed in section 4.3) or controlled processes were occurring. Authors reported that even in the FTD group, only low levels of FTD were detected. This may have had some bearing on the results.

Table 1.5 *Review of Studies Finding Hyperpriming*

Study	Participants	SOA	Relatedness proportion	% Words	TD Rating	Word pair relationship	Task type
Study 1. Manschreck et al. 1988	12 FTD 9 non TD 11 Controls	250ms	20%	40%	SADS	Associated	Lexical Decision Word Pairs
Study 2. Spitzer et al. 1993	21 FTD 29 non TD 50 Controls	200ms	33%	50%	BPRS	Direct and Indirect	Lexical Decision Word Pairs
Study 3. Moritz, et al. 2001a	16 FTD 28 non TD 30 Controls	200ms	50%	50%	PANADSS	Dominant and subordinate	Lexical Decision Word Pairs
Study 4. Moritz, et al. 2001b	15 FTD 30 non TD 30 Controls	200ms	55%	100%	PANADSS	Indirect	Word Pronunciation
Study 5. Moritz, et al. 2002	12 FTD 20 non TD 65 Controls	200ms	50%	100%	PANADSS	Indirect	Word Pronunciation
Study 6. Chenery et al. 2004	14 SZ 12 Controls	250ms or 500ms	33% or 75%	100%	TLC	Close and distant associates	Lexical Decision Word Pairs
Study 7. Quelen et al. 2005	20 SZ 20 Controls	500ms	-	50%	TLC	-	Lexical Decision Word Triplets
Study 8. Lecardeur etal. 2007	15 SZ 15 Controls	250ms	10%	50%	TLC	-	Lexical Decision Word Triplets

1.3.3.2 Review of the Literature Finding Normal Priming in FTD

Two studies have reported normal priming in FTD. Results of these studies are summarised in table 1.6.

Study 1: Blum and Freides (1995) examined priming in FTD using a lateralised version of the lexical decision priming task. Nine FTD and nine non FTD participants with schizophrenia were included as were eleven healthy controls. The TLC was used to rate FTD. Length of illness and

medication were not reported. The proportion of non-words was 25% as was the relatedness proportion. The SOA employed was 350ms and the length of prime presentation was 100ms. Word pairs were related by association, whether some of these pairs were also categorically related is unknown. Findings showed no significant differences between the control group and either the FTD or non TD group.

Study 2: Barch et al. (1996) used a word pronunciation task to examine priming and FTD. Included in this study were 25 individuals who were unmedicated, 75 medicated, 10 with a diagnosis of depression, and 28 healthy controls. The schizophrenia groups were matched for medication. The schizophrenia group was split based on a single item of the Brief Psychiatric Rating Scale (BPRS) known as 'conceptual disorganisation'. Word to non-word ratio and relatedness proportion were not available nor was the nature of the relationship between word pairs. Five SOAs (200, 300, 450, 700, and 950ms) were used to examine the influence of SOA on the priming of FTD individuals. The prime was presented for 100ms. Results showed that the presence of FTD did not impact on degree of priming at any of the SOA's.

Table 1.6 *Review of Studies Finding Normal Priming*

Study	Participants	SOA	Relatedness proportion	% Word	TD Rating	Word pair relationship	Task Type
Study 1. Blum & Freides 1995	9 FTD 9 non TD	350ms	25%	75%	TLC	Category	Lexical Decision Task
Study 2. Barch et al. 1996	34 FTD 66 non TD	200ms 300ms 450ms	-	-	BPRS	-	Word Pronunciation

1.3.3.3 Review of the Literature Finding Hypopriming in FTD

Three studies have reported hypopriming in FTD. Summaries of these studies are presented in table 1.7.

Study 1: Aloia et al. (1998) compared schizophrenia groups (FTD=9, non TD=11) and 21 healthy controls using a word pronunciation task. The TLC was used to measure FTD. Stimuli used were all categorically related and were separated into three groups based on their degree of association (high, medium and low). The relatedness proportion was 63%. Medication was not reported. Results showed that both the healthy controls and the non FTD group primed. The FTD group on the other hand did not demonstrate any priming in any of the three conditions. Authors concluded that this result occurred because the semantic memory networks of those with FTD have abnormalities in their spread of activation through the semantic networks.

Study 2: Besche et al. (1997) examined both semantic and syntactic function in two schizophrenia groups, FTD=24, non TD=10, and a number of control groups, psychiatric=14, hospitalised=20 and healthy=20. A lexical decision task with an SOA of 500ms and length of prime presentation was 250ms was used in both the semantic and syntactic condition. Semantic pairs were related via category or were synonyms or antonyms. The proportion of words to non-words was 66%

and 34% respectively and the relatedness proportion was 25%. FTD was evaluated using the TLC and those participants with a rating of seven or less were regarded as non TD and those with a rating above as FTD. The schizophrenia groups were matched on medication dosage but the FTD group were rated as having more severe symptoms. Results demonstrated that all groups except for the FTD group showed priming of related pairs. All groups demonstrated intact syntactic function. It was concluded that this finding reflected an absence in post-lexical processes in FTD.

Study 3: Passerieux et al. (1997) examined 22 individuals with schizophrenia (FTD=11 non TD=11) and 11 healthy controls using a lexical decision task. FTD was rated using the TLC in the same way as the above article. Medication level was not reported. Both categorical and semantic relations were included in the word pairs. The proportion of related pairs was 16.7%, the word non-word ratio was 50% and the SOA used was 500ms and the prime was displayed for 450ms. Results showed that priming occurred in both the control and non TD group. No priming was apparent in the FTD group.

Table 1.7 *Review of Studies Finding Hypopriming*

Study	Participants	SOA	Relatedness proportion	% Word	TD Rating	Word pair relationship	Task type
Study 1. Aloia et al. 1998	9 FTD 11 non TD 21 Controls	-	63%	-	TLC	Category and Associated	Word Pronunciation
Study 2. Besche et al. 1997	24 FTD 10 non TD 20 Controls	500ms	25%	66%	TLC	Category	Lexical Decision Task
Study 3. Passerieux et al. 1997	11 FTD 11 non TD	500ms	50%	16.7%	TLC	Category	Lexical Decision Task

1.3.3.4 Why the Difference in Outcome?

The majority of studies have reported increased priming or hyperpriming amongst those individuals with FTD i.e. eight of thirteen studies. This would seem to suggest that there is some validity to the hyperpriming theory. However, with regards to studies finding hyperpriming, authors of studies one to five are all from the same laboratory in Germany. It may be that some parameter or combination of parameters used in their lab is responsible for their hyperpriming results. These five studies offer a brief description of the stimuli used but do not include a list of the pairs they use. It may be that the stimuli being used are responsible for the finding of hyperpriming.

The hyperpriming study by Chenery (2004) also appears to be methodologically flawed. This study examined multiple variables including two different SOA's, two different relatedness proportions, four different degrees of relatedness between pairs, and two groups. In order to have sufficient power to make this many comparisons, a large number of participants would be required. Only 12 controls and 14 schizophrenia participants were included in this study. As such, this study has insufficient power. Before any firm conclusions can be made about the reality of the phenomenon of hyperpriming, all of the studies in the review need to be compared closely.

The type of FTD experienced by participants is another important factor which was not discussed in the studies above. As mentioned in Chapter One, there has been suggestion that the type of FTD exhibited by participants can influence results (Andreasen, 1979). Specifically, positive FTD is associated with increased priming whilst negative FTD has been related to normal or reduced priming (Moritz, Mersmann, Kloss, Jacobsen, Wilke, et al., 2001). It may be that those studies finding normal or hypopriming included more participants with negative symptoms. This is unlikely however, because

the only scale which includes negative FTD in its ratings is the TLC. The importance of the chosen scale is discussed next.

Only three out of the eight hyperpriming studies measured FTD using a scale specifically designed for this purpose (Chenery et al., 2004; Lecardeur et al., 2007; Quelen et al., 2005) whilst five of the studies relied on a single item from a general psychopathology scale to make their determination (Moritz, Mersmann, Kloss, Jacobsen, Andresen, et al., 2001; Moritz, Mersmann, Kloss, Jacobsen, Wilke, et al., 2001; Moritz et al., 2002; Spitzer, Braun, Hermle, & Maier, 1993). With regards to the two studies that found normal priming, one used the TLC which specifically evaluated FTD (Blum & Freides, 1995) whilst the other depended on a single item from the BPRS (Barch et al., 1996). All three studies which found hypo-priming used the TLC (Aloia et al., 1998; Besche et al., 1997; Passerieux et al., 1997). Given that the TLC was used in studies finding hyperpriming, normal priming and hypopriming, the results cannot be attributed to the rating scale used.

It is also important to point out that in the study by Manschreck et al., (1998) the FTD group not only displayed hyperpriming for the related pairs, they also demonstrated faster RT in general when compared to the control group; a finding that is atypical in itself (Goldberg & Weinberger, 2000) and suggests that there may be some methodological flaw in the study which cannot be easily identified.

It is also interesting to note that three of the eight studies reporting hyperpriming at the automatic level also reported normal priming for the schizophrenia groups at the controlled level (Lecardeur et al., 2007; Quelen et al., 2005; Spitzer, Braun, Hermle, & Maier, 1993). This is in contrast with the majority of research that supports the notion that controlled processes are impaired in

schizophrenia (Besche et al., 1997; Minzenberg et al., 2002). A closer examination of the study by Spitzer suggests some methodological flaws in the study. Spitzer reported that some priming results were only significant when priming was calculated by subtracting the RT to unrelated pairs from the RT to related pairs. As discussed previously, this method of calculating priming can lead to the illusion of hyperpriming. When priming was calculated using the percentage of priming method, these significant results disappeared. It is difficult to compare the findings of Quelen et al. (2005) and Lecardeur et al. (2007) to other studies in the FTD/priming literature. The reason being that these two studies employed a triple word priming task; the implications of this form of priming study are not yet clear.

The relatedness proportion used in the studies which find hyperpriming is of concern. As discussed previously, a low proportion of related word pairs are required to ensure that automatic and not controlled or postlexical processes (such as semantic matching) are being elicited. The review by Rossell and Stefanovic (2007) found that a low relatedness proportion (up to 25%) generally resulted in normal or decreased priming in schizophrenia whilst a higher relatedness proportion (over 25%) produced a greater degree of priming amongst the schizophrenia groups. This distinction was found to be true independent of SOA. This suggests that relatedness proportion might affect those with schizophrenia differently from the way in which it affects controls. It may be that individuals with schizophrenia are able to make better use of a high relatedness proportion via semantic matching as a compensatory strategy. Of the eight studies reporting hyperpriming, Manschreck et al. (1998) Chenery et al. (2004) and Lecardeur et al. (2007) were the only ones who kept their relatedness proportion at a low enough level (20%, 25% and 10% respectively) to reduce the likelihood that controlled or postlexical processes were having an impact on priming. As mentioned previously, it is hard to

compare the study by Lecardeur given that there were two primes and one target used rather than simply pairs of words. In addition, the study by Chenery has significant power issues and so its conclusions cannot be relied on.

Of the studies that found normal priming, one used a 25% relatedness proportion (Blum & Freides, 1995) and the other did not give its relatedness proportion (Barch et al., 1996). Of the studies that found hypopriming, one used a high proportion of 63% (Aloia et al., 1998) and two used lower proportions generally used to reduce the likelihood of controlled processes affecting results (Besche et al., 1997; Passerieux et al., 1997). Given the heterogeneity of proportions amongst studies with different findings, there is no clear evidence that relatedness proportion alone is responsible for the variation in results.

The review by Rossell and Stefanovic (2007) did not examine the role of non-word ratio. It is possible that the postlexical function of semantic matching played a role in the results of the FTD studies, thus the non-word ratio will be examined. As discussed previously (see section 4.3), a high proportion of non-word pairs can encourage semantic matching which speeds up response to semantically related pairs and could thus falsely inflate priming scores. It is also generally found that when this process occurs, a greater number of unrelated word pairs are falsely classed as non-words by participants. Because error rates are not reported for these studies, it is not possible to determine whether this process has played a role in the outcome. The eight studies finding hyperpriming all used a non-word ratio of around 50%. Given that in his review of semantic priming literature Neely (1991) found that automatic processing could be successfully elicited using a non-word ratio of 50%, it is unlikely that this factor is responsible for the finding of hyperpriming.

There is a common acceptance in the literature that participants with schizophrenia do not demonstrate priming at the controlled level (Besche, 1997; Minzenberg et al., 2002). Two of the three studies that found hyperpriming under automatic conditions also found priming in the controlled condition (Lecardeur et al., 2007; Spitzer, Braun, Hermle, & Maier, 1993). This may suggest that there is a feature of both of these experiments that is inflating priming giving the false impression of hyperpriming at both the automatic and controlled level. The schizophrenia groups were affected differently across these two studies. In the study by Lecardeur et al. (2007) both the FTD and the non TD group demonstrated increased priming whilst in the study by Spitzer et al. (1993) a different pattern of priming was found between the FTD and non TD group. The lack of difference in priming between the FTD and non TD group in the Lecardeur study may be related to the fact that they detected only very low levels of FTD in their FTD group. Spitzer's controlled processing condition differed from his automatic processing condition in terms of SOA only. As discussed previously, SOA alone is not responsible for determining whether automatic or controlled processes occur. In addition, factors such as instructions and relatedness proportion are also important in determining which form of processing is occurring. Given that it is more common to find intact priming under automatic rather than controlled conditions, it is likely that controlled processing was not occurring in either condition. As mentioned previously, the study by Lecardeur used word triplets rather than pairs and thus it is difficult to make comparisons to other studies and to the general guidelines on semantic priming.

Despite the shortcomings of these studies, the variables of manipulation have been the same for the non TD and the FTD group in the independent studies, and therefore are unlikely to explain why these two groups are differing. A variable which would affect these groups differently is medication.

An examination of the studies reveals that medication is not always recorded separately for the two groups and when it is, it is always matched. It is therefore unlikely that medication differences is not responsible for the finding of hyperpriming amongst FTD groups.

The type of task used has not influenced the results. Both the WPT and the LDT task were able to elicit the hyperpriming effect. Both tasks have also revealed normal priming and no priming. As such, task choice does not appear to be a factor in the results.

The review by Rossell and Stefanovic (2007) showed that associatively related word pairs can elicit a greater degree of priming than categorically related word pairs in schizophrenia. An examination of the eight studies reporting hyperpriming reveals that a majority of them used associative relations, or at least included some associative relations in their stimuli sets. Some studies included indirectly related pairs (Moritz, Mersmann, Kloss, Jacobsen, Wilke, et al., 2001; Moritz et al., 2002; Spitzer, Braun, Hermle, & Maier, 1993) and although all stimuli are not available to examine, it is likely that at least some of the pairs shared an associative relationship. Lecardeur et al. (2007) used both attribute and associative relationships. Moritz et al. (2001) examined rhyming pairs and semantically related pairs and included targets that reflected the dominant or subordinate meanings of a prime (some of which would invariably have included associates). In terms of studies that reported normal priming, Blum and Freides (1995) used associatively related pairs, whilst Barch, et al., (1996) did not report the nature of the relationship between the pairs included in their experiment. All three studies that found hypopriming included categorically related pairs in their stimulus set. Aloia et al. (1997) used only category related words, Besche, et al. (1997) used category relations and the antonyms and synonyms of words (these relationships can be considered associated in nature). Lastly,

Passerieux, et al. (1997) used categorical relations amongst their stimuli. This review reflects the finding by Rossell and Stefanovic (2007) with hypopriming more likely to occur with categorical stimuli and normal or hyperpriming being the more likely scenario with associated stimuli.

As can be gathered from this review, there are multiple varying factors that may be contributing to the myriad of priming results evident in the literature. At this point, it is not clear which factors are influencing results. It may be that a certain number of these factors need to be organised in a specific way to elicit hyperpriming. For example, the use of associatively and indirectly related pairs with a high relatedness proportion. This review provides an update of the work by Kerns and Berembaum (2002). Unlike the result of that review, on this occasion, there are more studies finding hyperpriming. Despite this increase in studies reporting this finding, hyperpriming it is still far from confirmed. In fact, in conclusion to this review, it remains unclear whether hyperpriming reflects a real phenomena in FTD or whether it is the result of methodological issues.

Table 1.8 *N400 Priming Effects Across SOA's*

	N400 effect (SOA 350)	N400 effect (SOA 950)	Behavioural prime (SOA 350)	Behavioural prime (SOA 950)
Control	Y	Y	Y	Y
Medicated SZ	Y	N	Y	Y
Unmedicated SZ	N	N	Y	Y

Research examining priming in unmedicated SZ patients is rare. One paper examined the N400 effect as well as behavioural priming for unconscious and consious priming and found that priming was statistically significant behaviourally for the unmedicated group whilst N400 effects were not significant in any condition. The medicated patients had significant N400 effects in the unconsious priming but not for the conscious priming condition. Overall, this data suggests semantic function is more abnormal without medication (Condray, Siegle, Cohen, van Kammen, & Steinhauer, 2003). Another study looking solely at behavioural data found no significant effects for medication when priming calculations took general slowing into account (Barch et al., 1996).

1.3.5 Delusions

Delusions are a hallmark of psychotic illness. They are defined in the DSM-IV-TR as "erroneous beliefs that usually involve a misinterpretation of perceptions or experiences" (Association, 2000, p. 299). Different delusional themes exist and within schizophrenia/schizoaffective disorder with 30% of delusions are associated with grandiose or religious themes and around 60-70% describe delusions of reference or persecution (Gilleen & David, 2005). Appelbaum, Robbins and Roth (1999) identified the following delusions: (1) persecutory, (2) body and mind control, (3) grandiose, (4) thought broadcasting, (5) religious, (6) guilt, (7) somatic, (8) influence on others and (9) jealousy. In

addition, thought broadcasting, thought insertion, thought withdrawal and thought control have also been described as Schneiderian delusions (Cohen & Junginger, 2006).

In their review of delusion research, Gilleen and David (2005) identified a number of broad domains of research into the cognitive aetiology of delusions. These areas included reasoning abnormalities (probabilistic reasoning/jumping to conclusions) (Garety, Hemsley, & Wessely, 1991), emotion (emotion mediating imagined versus real events) (Freeman, Garety, Kuipers, Fowler, & Bebbington, 2002) attributional bias (externalising biases for negative events) (Bentall, 1994), theory of mind (understanding the motives and thoughts of others) (Frith, 1994), and more recently, deficits in semantic memory, which have been highlighted in the development and maintenance of delusions (McKenna, 1991; Rossell et al., 1999; Tamlyn et al., 1992). Each of these theories is discussed below.

1.3.6 Theories of Delusions

1.3.6.1 Probabilistic Reasoning

Garety and Hemsley are the main contributors to the theory that delusions are the result of a probabilistic reasoning bias (Garety & Hemsley, 1994; Garety et al., 1991). The focus of this theory is on the maintenance of delusions rather than their cause, as they suggest that the causes may vary widely (Garety & Freeman, 1999). This theory incorporates aspects of self esteem, perception and motivation. Support for this theory comes from 'jumping to conclusions' tasks in which deluded participants are shown to request less information before reaching a judgement than non-deluded and healthy control participants (Moritz & Woodward, 2005). Further tasks have been used to confirm this finding including tests of probability estimation, inductive reasoning and data gathering (Garety &

Freeman, 1999). Garety and Freeman's 1999 review found that 11 of 14 studies provided support for a reasoning bias in delusions in psychosis. This was clarified however, with authors reporting that the pattern of response was more consistent with a data gathering bias as clinical group's demonstrated normal performance with structure or guidance. In addition, more recent studies have shown that the reasoning bias in those with paranoid delusions or tendencies (Freeman, Pugh, & Garety, 2008) which calls into question whether this unified theory of delusions can account for all the different types of delusions.

1.3.6.2 Attributional Bias/ Persecutory Delusions as a Defence

An attributional bias describes the tendency to attribute positive events to the self and negative events to outside source (Blackwood, Howard, Bentall, & Murray, 2001). This self-serving tendency is normal in healthy individuals to a degree but research in SZ demonstrating that this bias is exaggerated. This exaggeration has been measured using attributional questionnaires and studies of overt and covert self-esteem. This exaggerated self-serving bias has been interpreted to exist as a means of maintaining self-esteem (Bentall, 1994) as measures of overt and covert self-esteem have supported a relationship between the bias and self-esteem function (Garety & Freeman, 1999). In their 1999 review, Garety and Freeman confirmed that there was evidence that delusions were related to attributing negative events to others but specifically when material was related to self-referent material. There was not sufficient evidence however, to suggest that this bias was related to self-esteem maintenance.

1.3.6.3 Delusions and Emotion

Some authors have focused on the relationship between the content of delusions and emotional state (Freeman et al., 2002). Freeman extended the probability bias work of Garety by incorporating evidence from anxiety literature. The interest in anxiety stemmed from the fact that the content of anxious and persecutory thoughts is similar. They are both concerned with danger, whether physical or psychological. He suggests that anxiety and emotion need more emphasis in a reasoning theory. This model incorporates attributional bias elements from Bentall's approach, but suggests that persecutory delusions are not a defence. Instead, they are based on the emotions of the individual. That is, the delusions are consistent with the individuals mood and world view. In its simplest form, this collaboration of theories suggests that as a result of a negative trigger, anxiety occurs and reasons for negative experiences are sought. These reasons are based on the individual's ideas and views about the world (semantic memory involvement). If the search for meaning based on personal knowledge is mediated by a tendency to jump to conclusions, to naturally attribute negative events to others, and a failure in theory of mind thinking, then conclusions will be anomalous. This anomaly may be expressed as a persecutory delusion. The most novel aspect to this theory is the incorporation of anxiety. In addition to the face value of postulating a link between delusional thinking and anxious thinking, the authors cite longitudinal studies showing that children who went on to develop psychosis demonstrated significantly more anxiety as children than did those who did not.

1.3.6.4 Theory of Mind

The term theory of mind (ToM) refers to the ability to understand one's own and other persons' mental states including their thoughts, emotions and beliefs (Brune, 2005). This term was first used in the 1970's in relation to understanding deception in chimps (Frith, 1994) but has since been used to examine human understanding in the areas of autism, frontal lobe damage and schizophrenia (Brune,

2005). The intriguing aspect of the ToM explanation is that it is able to explain various psychotic symptoms (Frith, 1994). For example, psychotic profiles characterised by negative symptoms have been likened to autism with individuals demonstrating social withdrawal, flat affect and poor social function generally and this symptom profile has been predicted to relate to poor ToM function. Thought disorder is thought to reflect a failure to understand that others do not have the same points of reference as the speaker and alien control and thought insertion are thought to stem from a difficulty in understanding and monitoring ones own intensions. Finally, delusions are thought to represent a misunderstanding of ToM both in the self and others. This leads to false ideas about the thoughts and intentions of others which then manifests as delusions of persecution. In their review of ToM studies in psychosis, Garety and Freeman (1999) found support for an association between increased symptoms and ToM deficits but only weaker evidence for an association between deficits in this area and the presence of delusions. Indeed ToM deficits are confounded by their association with general cognitive function in many cases.

1.3.7 Delusions and the Semantic Network

This semantic memory theory is of particular interest to the current thesis and will be explored in greater detail than the previous theories. Bleuler postulated that the loosening of associations of thought and speech might contribute to the development of delusions. This idea has been taken further by researchers including McKenna (1991) and Rossell (1999) who make a link between semantic memory deficits and delusions. McKenna proposed one of the earliest definite links between delusions and semantic memory (1991). In its simplest form McKenna suggested that semantic memory is the storage place for meaning and belief and as a result, deficits in the structure or function of this system might reasonably lead to abnormalities in these areas which could be expressed as delusional thought.

More meaningfully, if there develops an abnormality in the use of semantic memory, this will, over time, affect the structure of this system (although it is more stable than episodic memory it is still dynamic and changeable). As such, perception or cognitive problems affecting the processing of information might lead to abnormalities in the creation of semantic memories. In addition, should these abnormalities remain; further information over time will confirm the new deficient memories. These new memories may also, over time, corrupt previously well-established semantic memories by repeatedly providing evidence in contradiction of previously accepted information. An account supported in more recent work by Rossell and colleagues (2008).

This semantic explanation of delusions has not received much attention, thus it was not included in the Garety and Freeman (1999) review. Therefore, the empirical studies published so far will be reviewed here. Rossell et al. (1998) used a sentence verification task (silly sentences task mentioned in previous chapter) to investigate semantic memory in schizophrenia. Significant differences between the control and delusional individuals were found on nonsense sentences with persecutory and religious themes. Delusional participants were more likely to incorrectly accept nonsense sentences that had an emotional content congruent with delusional beliefs (e.g. A cactus can bite) and also unlikely sentences (e.g. Politicians may have four wives) even when their content was not congruent with their delusions. A later study by the same group (Rossell et al., 1999) investigated verbal fluency and delusions. This study found that phonological (non-semantic) fluency was intact in delusional participants while semantic fluency specifically was impaired compared to healthy controls and schizophrenia participants without delusions. Further, an examination of the pattern of semantic output revealed poor semantic organisation in those with delusions. The authors interpreted such findings as evidence for difficulty in access and storage of semantic information among deluded

individuals. The next study by Rossell and colleagues examined semantic priming in delusions (Rossell & David, 2000). They found that delusions were associated with abnormal processing of emotional words (inhibition instead of facilitation). Kiang, Kutas, Light and Braff (2008) examined direct and indirect priming using EEG and found that delusions were related to more abnormal processing of semantic pairs.

A problem in this field is that studies looking at semantic memory's relationship to FTD have reported that FTD was the only psychotic symptom to significantly relate to deficits in semantic memory (Tamlyn et al., 1992). Further, other authors have found no association between delusions specifically and semantic priming task performance (Spitzer, Braun, Hermle, & Maier, 1993). Given the recent literature by Rossell and McKenna however and given the significant relationship often found between thought disorder and delusions (discussed next), it is reasonable to continue this investigation.

1.3.6.6 Relationship between Delusions and Formal Thought Disorder

Bleuler (1911/1950) suggested that delusions relate to a 'loosening of associations' which includes/describes many positive FTD symptoms (Mortimer et al., 1996). More recently, Cutting and Murphy (1988) described delusions as a symptom of TD. This definition encompassed both delusional thought and our more current understanding of FTD. The theoretical link between these two concepts is therefore reasonably established. Despite this however, there is little research that has tried to explain experimentally what this link is. The failure to explore this relationship may stem from its complexity for example, not all individuals with delusions have FTD and vice versa (Goldberg et al., 1998) and according to Liddle (1987) these symptoms load on different syndromes with delusions

loading on a “reality distortion syndrome” while FTD loads on a “disorganisation syndrome”. Some studies have found no correlation between the two symptoms (Andreasen & Olsen, 1982) however it is not uncommon for research to find a significant positive correlation between the two (Mortimer et al., 1996). Mortimer et al. (1996, p. 289) reported that “there was some suggestion of a complex interaction between delusions, formal thought disorder, and semantic memory impairment”. While there has been substantial research on the relationship between FTD and semantic function and now, a growing body of work examining delusions and semantic function, little has been done to explore the relationship between the two symptoms and their relationship to semantic memory. This relationship will be explored in the current thesis.

1.4 Creating a Priming Experiment

For the purpose of this thesis, unless otherwise specified, any reference to ‘priming’ refers to semantic priming. The semantic priming paradigm has been used extensively over the years. It is from the results of such experiments that many of the above mentioned theories are derived (Plaut, 1995). In a typical lexical decision task (which is one method of assessing semantic priming), a pair of words is presented in the centre of a computer screen, one after the other. The role of the participant is to determine whether the second word of the pair is a real word. Participants are generally required to respond with both hands using a button press. In some experiments, a response is only required when the second word is real. In others, participants must press one button for real words, and another button for pseudo words (Neely, 1991). When a word to be recognised (i.e CAT) has been preceded by a semantically related word prime (i.e DOG), RT to this pair is faster compared to the RT to an unrelated

pair (Chiarello, 1995). While the experimental set up itself is simple the creation of the task to be presented is a far more complicated. Task creation is discussed below.

1.4.1 Automatic (Implicit) and Controlled (Explicit) Priming Processes

There are three different types of processing that can be elicited in participants. These include automatic, controlled or post lexical processes. Each of these different forms of processing can be elicited depending on the parameters of the priming experiment design. As the name suggests, automatic processing occurs due to experimental manipulations which lead to automatic and unconscious processing. Posner and Snyder (1975) define automatic attentional processing as being reliant on past learning, unlimited in capacity and as a process that occurs without awareness or intention. In addition, they propose that it does not interfere with other ongoing mental activity. For the purposes of this thesis, implicit and automatic processes can be regarded as synonymous. Results of automatic priming are associated with facilitation to related pairs. Facilitation refers to the finding that participants are faster in responding to related word pairs in comparison to unrelated word pairs (McNamara, 2005). Automatic processing experiments allow researchers to examine the organisation of the semantic memory system without the confounding effects of higher level cognitive functions. The experimental manipulations required to encourage these different forms of processing are discussed next.

Controlled processing, unlike automatic processing, occurs with awareness. This form of processing allows participants to consciously work their way through the experiment. Controlled processing is limited in its capacity and can therefore only be directed to a limited number of items at one time. Because concentration is required, distractions or other ongoing mental activity can interfere

with performance. Controlled processing may be regarded as the same as explicit processing when the task is associated with instruction to search for/ recognise semantic relatedness between pairs. Controlled processing allows researchers to examine the way in which higher level cognitive processes affect access to semantic memory. When the experiment is manipulated to maximise controlled processes then both facilitation and inhibition can occur (McNamara, 2005). In a controlled priming experiment, three types of word pairs are included; related pairs, unrelated pairs and neutral pairs (often these pairs include made up words such as GLUB). Generally it is found that reaction time is quickest to the related pairs. Response time is next fastest in response to the neutral pairs and finally, slowest in response to unrelated pairs. In a controlled processing experiment, neutral pairs often act as a baseline. Facilitation and inhibition are calculated from this baseline measure. Facilitation is calculated as the time taken to respond to related pairs subtracted from the time taken to respond to unrelated pairs. Inhibition on the other hand, is calculated as the time taken to respond to neutral pairs minus the time taken to respond to unrelated pairs. In controlled experiments, participants are informed that they will see related pairs among the stimuli. In addition, there is often a larger proportion of related than unrelated pairs included in the stimulus set. These two factors encourage controlled processing. As a result, participants develop a general expectation that if the target is a real word, it should be related to the prime. If they are presented with a target that is not expected (an unrelated target), participants response rate is slowed or 'inhibited'. See Figure 3 below for a summary of the differences between automatic and controlled processing.

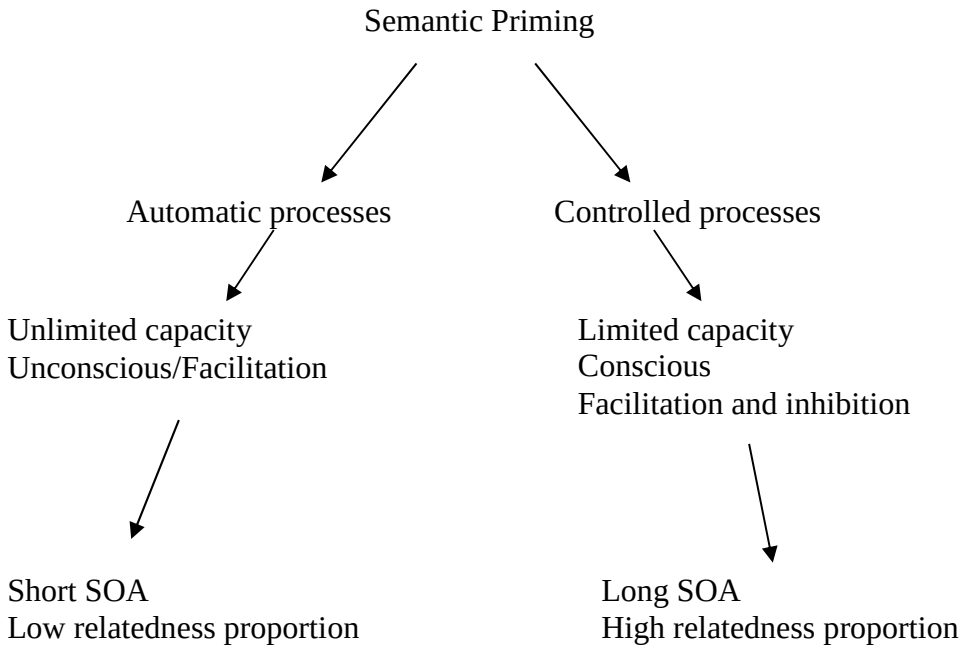

Figure 1.4 Automatic Versus Controlled Processing

Controlled processing can occur as a result of pre lexical processing (before the presentation of the target) or post lexical processing (after presentation of the target). Expectancy is an example of a pre lexical process. Expectancy is when the participant activates a set of possible targets in their mind based on the expectation that the prime and target will be related. If the target matches the expectancy set, facilitation will occur. Inhibition occurs when the target does not match the participants expectancy set. It describes the extra time taken to process the fact that the target was not what was expected plus the time taken to process what the target actually is.

Semantic matching is an example of a post lexical process (Neely, 1991). And can occur without awareness. Semantic matching describes a participant's ability to match the target with the prime based on semantic relatedness.

There are three task parameters which determine the level of involvement of these processes. These include the length of time between presentation of the target and prime, known as the stimulus onset asynchrony (SOA), the proportion of related pairs to unrelated, neutral and pseudo word pairs, and the instructions given to participants. These are reviewed below:

1.4.2 Stimulus Onset Asynchrony

Stimulus onset asynchrony (SOA) describes the time between when the prime is first presented to the time when the target first appears on the screen. A short SOA is often employed to encourage automatic processing. There are no hard and fast rules regarding what constitutes a short or long SOA; although, a review by Rossell and Stefanovic (2007) found that a majority of studies which successfully invoked automatic processing (evidenced by a lack of inhibition) used an SOA of less than 500ms. The reason this results in automatic processing is because a short gap in between the presentation of the prime and target does not allow the participant time to consciously consider their decision or recognise the relationship between the pair. A long SOA on the other hand (> 500msec) does allow for conscious processes to take place. The length of the presentation of the stimuli themselves, irrespective of the SOA, is also a matter of interest. It is a generally accepted finding that individuals with schizophrenia are slowed in their speed of processing (Quelen, Grainger, & Raymondet, 2005). As a result, they need a reasonable amount of time to perceive a stimulus and if this is not provided, it is possible that no priming will occur.

1.4.3 Proportions of Pairs

Both the relatedness proportion and the non-word ratio are important factors when considering the results of an experiment that has utilised a lexical decision task (LDT). Relatedness proportion

refers to “the probability that a word target will be related to its prime” (Thompson-Schill., Kurtz, & Gabrieli, 1998, 447-448). The non-word ratio refers to “the probability of a target’s being a non-word” (Neely, 1989, 1010). It has been shown that increases in either the relatedness proportion or the non-word ratio can lead to an increase in the degree of priming elicited. This is due to increases in the occurrence of semantic matching (discussed in section 1.4.1). Semantic matching is a strategy used to predict the nature of the relationship between a prime and its target. When the instructions for a priming experiment direct the participant to categorise the target word as a real word or a made up word, semantic matching can be a useful strategy. For example, if most of the word-word targets are related, the semantic matching strategy dictates that the presence of a relationship between a prime and its target is enough to determine whether the target is a real word. As such, all related pairs are judged to be word pairs and other word pairs are categorised as non-word pairs. The downside to using this strategy is that unrelated word pairs are among those classified as non-words. When the non-word pair ratio is high, the more common finding of an absence of a relationship between words will also encourage the use of semantic matching but in a different way. In this case, the semantic matching strategy dictates that when no relationship is detected between prime and target, that pair will be treated as a non-word pair. Once again, unrelated pairs are incorrectly categorised as non-word pairs (Neely, 1989; Thompson-Schill, et al., 1998). Unfortunately, few studies examine their error data to determine whether such factors have influenced their results.

Importantly it is thought that relatedness proportion affects prelexical processing whilst non-word ratio may be related to postlexical or controlled processing (Thompson-Schill. et al., 1998). At longer SOA’s an increase in the number of related word pairs to unrelated word pairs leads to a greater degree of priming.

To maximise the likelihood that automatic processing occurs, the proportion of unrelated and non-word pairs is made larger than the proportion of related pairs. There are no strict rules for determining what percentage of each type of word pair is appropriate. Generally speaking, researchers have used 20-30% related words, around 30-40% unrelated and around 50% pseudo words. This low percentage of related word pairs reduces the likelihood that the participant will recognise that there are related pairs amongst the stimuli. When controlled processing is desired, researchers will often increase the percentage of related pairs. Instead of a 20-30% relatedness proportion, the proportion is set at above 50% (Neely, 1991). The nature of the relationship between the words of the pairs themselves also has a significant impact on priming results.

1.4.4 Word Pair Relationship

The manner in which word pairs are deemed to be related (phonologically, associatively or categorically) also has an impact on the way in which words are processed (Collins, 1999) (see Table 1.5 for types of pairs and examples). A phonological relationship describes two words that sound the same i.e. CAT-BAT. As the name suggests, an associated pair of words are related because the two words/concepts often occur together. Categorically related pairs require that the two words fall into the same category. Word pairs can also be both categorically and associatively related. There are some occasions when ambiguous word pairs exist. Ambiguous pairs include a prime word which has two meanings. There is usually a dominant and a subordinate meaning for the prime. The relationship of the prime to target in ambiguous pairs may be categorical or associative. This is further complicated by the fact that not all category or associatively related pairs are equal. For example, CAR would be dominant under the category of TRANSPORT while CANOE would be less dominant. In terms of

associatively related pairs, the words SNAKE and BITE are more closely associated then SNAKE and COIL. The result of which is that the dominantly related category pair (TRANSPORT-CAR) and the stronger association (SNAKE-BITE) would result in larger priming effects than would the alternative pairs (TRANSPORT-CANOE, SNAKE-COIL) (Burgess & Simpson, 1988; Collins, 2002).

Table 1.9 *Pair Relationships in Semantic Priming*

Word Pair Relationship	**Prime**	**Target**
Associated	Bull	Fight
Category	Arm	Head
Associated + Category	Arm	Leg
Ambiguous Dominant	Kid	Child
Ambiguous Subordinate	Kid	Goat
Indirect	Lion (Tiger)	Stripes
Phonological	Cat	Hat
Unrelated	Dog	Fairy

Different word pair relationships have different effects on priming. Phonologically related words can result in priming even when the two words are not semantically or categorically related. Generally speaking, associatively related pairs result in larger priming effects than do categorically related pairs (Neely, 1991). These issues need to be taken into account when designing a priming experiment. For example, Neely's (1991) review compared the available literature examining

controlled processing using different types of word relationships. It was found that when a large number of stimuli used are made up of associatively related pairs, then the magnitude of priming is much greater than the magnitude of inhibition, a pattern known as facilitation dominance. When a large number of the stimuli are made up of pairs of words that belong to the same category, then the degree of priming is small and the degree of inhibition is large, a pattern known as inhibition dominance.

1.4.5 Word Frequency

Word frequency is defined as the incidence of a word per one million words in a given language (Kwapil, Hegley, Chapman, & Chapman, 1990). Word frequency has a significant impact on priming effects. When a low frequency prime or target is included in a word pair, RT is increased. This is because when a word has a lower frequency, it is harder to access. Other features related to word frequency including imageability, concreteness, length, and familiarity are generally matched in experiments. Research suggests that features like word frequency and others like imagiability and concreteness can all affect priming (Samson & Pillon, 2004; Schwanenflugel & Akin, 1994). For the purpose of this thesis, these variables were matched across all pairs.

1.4.6 Lexical Decision Task and Word Pronunciation Task

The lexical decision task (LDT) will be used in this thesis and was described in the introduction to this chapter (see Figure 4). The word pronunciation task (WPT) is similar but in this task the participant is expected to read each word of the pair aloud instead of a pressing a button press. Neely's (1991) review of the priming literature suggests that there are a number of significant differences in the degree of priming found depending on whether the LDT or the WPT was used. Generally, it has been

found that the LDT results in larger priming effects than does the WPT. It was also found that there was evidence of priming when examining either high dominance (BIRD-ROBIN) or low dominance (BIRD-PENGUIN) pairs when the LDT was used but only priming for high dominance pairs when WPT was used. The phenomenon of backward priming (PAN-BED) has been found to occur in the LDT task but not in the WPT. The inhibition effects identified in LDT tasks are not present in WPT. Non-words are generally not used in pronunciation tasks due to concern that they would facilitate non lexical processes which might diminish priming effects. The following discussion is relevant to the LDT but not necessarily relevant to the WPT.

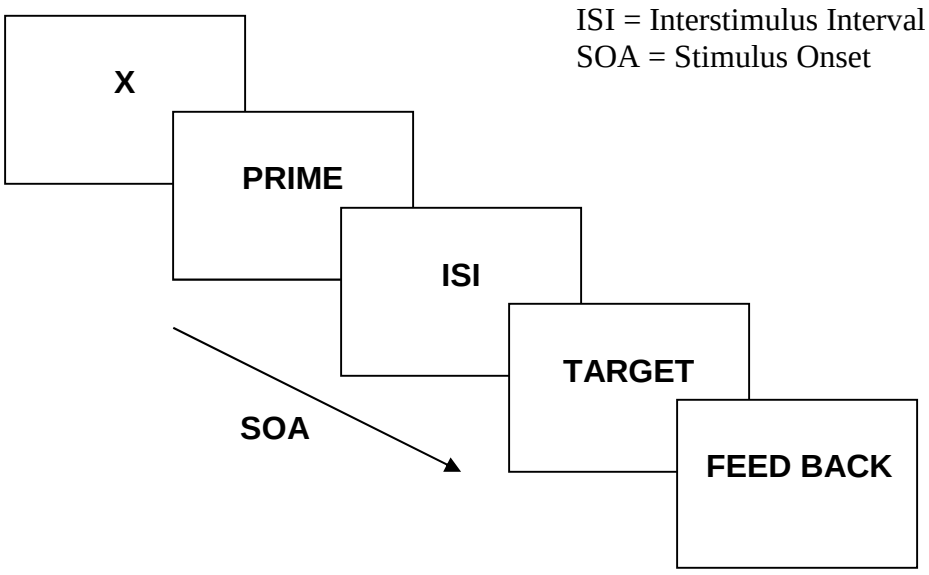

Figure 1.5 The Lexical Decision Task

1.4.7 Baseline

The stimuli used in a semantic priming experiment can include: related pairs, unrelated pairs, neutral pairs, and pseudo word pairs (Neely, 1991). The related stimuli are needed to elicit the priming

effect. RT is decreased when the words of a pair are related (CAT-DOG). The unrelated list includes pairs of words with no relationship between them (CANOE-BANANA). The unrelated pairs provide the comparison from which priming can be estimated. The time it takes to respond to a related pair subtracted from the time it takes to respond to an unrelated pair equals the degree of priming. Problems with this simple method of priming calculation have been identified. When controlled processing is elicited, inhibition can occur in reaction to the presentation of unrelated pairs (explained in section 4.1). To overcome this problem, many experiments have included a neutral baseline instead. A neutral baseline can include a row of X's or a word like 'blank' or 'neutral'. Unfortunately, this alternative baseline is not fool proof either. The neutral baseline pattern/word is repeated often and a number of criticisms of its use have been raised as a result (McNamara, 2005; Neely, 1991). One criticism is that due to its repetition, the neutral prime it may be easier to process, reducing RT and falsely decreasing priming for related pairs. Alternately, it might fail to alert the participant because it has been repeated and increase RT falsely suggesting a greater degree of priming for related pairs. Pseudo word pairs consist of a real word followed by an orthographically legal non-word meaning a word that can be pronounced and appears to be a real word, but is not (DRINK-SENO). These pairs are of no value beyond providing participants with a task. This is explained in more detail in the following paragraph.

1.4.8 Task Instructions

To elicit unconscious/automatic processing, participants must not be made aware of the presence of related pairs amongst the stimuli. To discourage such an observation, non-word pairs are included in the stimulus set. By directing the participant's attention to the fact that some words in the stimuli set are false, the experimenter is able to distract the participant from the true focus of the task.

In the instructions to participants, no reference is made to the presence of related words amongst the pairs. Instead, participants are simply instructed to press a button if the second word of the pair is a real word and to withhold their response if the second word is a pseudo word. Although the role of the participant in controlled versions of priming tasks are the same, the instructions given are quite different. Once again, participants are asked to press a button when the second word is real; however, participants are also informed that there will be both related and unrelated word pairs amongst the stimuli. This piece of information directs the participant's attention to these pairs increasing the likelihood that conscious processing will occur.

1.4.9 Calculation of Priming

Evidence suggests that the way priming is calculated can have a significant impact on the degree of priming found. The simplest way to calculate priming is to subtract the RT to related pairs from the RT to unrelated pairs with the difference representing the degree of priming elicited. It is a generally accepted finding that individuals with schizophrenia are slower in their performance on priming tasks (and many other cognitive tasks). When the speed of RT to unrelated pairs is subtracted from the RT to related pairs for schizophrenia groups, the difference is often larger than that found for control groups. This is based on the general principle that when participants are given two tasks that take different times to complete, there tends to be a positive correlation across participants between the raw latency difference scores and generalised slowness. For priming studies, this correlation is between 0.5 and 0.55 (Chapman, Chapman, Curran, & Miller, 1994). In studies reporting hyperpriming (greater priming in schizophrenia compared to controls) it is pertinent to ensure that such inflation is not responsible for results. A number of different methods are used to correct for this inflation. Some author's use a regression analysis model proposed by Chapman, Chapman, Curran and

Miller (1994) designed to test whether degree of priming is increased substantially based on generalised slowing (Barch et al., 1996; Chenery et al., 2004; Moritz, Mersmann, Kloss, Jacobsen, Andresen, et al., 2001; Moritz, Mersmann, Kloss, Jacobsen, Wilke, et al., 2001). Others use the percentage of priming obtained (Gouzoulis-Mayfrank et al., 2003; Nestor et al., 2006; Spitzer, Braun, Hermle, & Maier, 1993; Weisbrod, Maier, Harig, Himmelsbach, & Spitzer, 1998) and still others rely on the median RT rather than the mean RT (Aloia et al., 1998; Blum & Freides, 1995; Passerieux et al., 1997). It is not clear which one of these methods is best (Rossell & Stefanovic, 2007). For the purposes of this thesis, the percentage priming score will be used if one participant group or one experimental condition is characterised by slowing.

As this review demonstrates, there are numerous factors which need to be taken into consideration when creating a semantic priming task. To do so is a long and complicated task, and it is imperative that it is done with care to ensure that the results found reflect the processes of interest to investigators. The difficulties that arise when such processes are not carefully controlled and considered will become clear in the next chapter.

1.4.10 Word Lists

Four different word lists were created for the direct and indirect semantic priming tasks. Multiple lists were required because participants were seen on two occasions. Creating and counterbalancing lists requires careful consideration. Different word conditions (related v. unrelated) should differ in as few ways as possible. One way to do this is to use each word in both the related condition (LION-TIGER) and again in another list in the unrelated condition (LION-CHAIR). Importantly, you do not want the same person to see the word LION in both conditions because of the

confounding influence of repetition. Instead, it is generally accepted that a Latin square design be used to counterbalance the stimuli (McNamara, 2005). The number of lists created using this design is dependent on the number of variables you are interested on. For the direct experiment, we varied two conditions:

1. Whether pairs were related or unrelated
2. Whether there was a long or short SOA

These two conditions each have two alternatives, as a result, four lists needed to be created for the direct task and four lists for the indirect task. These lists were balanced for frequency, word length and concreteness.

1.4.11 Data Trimming

The method by which data should be trimmed is a complicated area with different papers employing different methods. Some use pre-determined cut offs for all participants regardless of group allocation or individual performance (Aloia, et al., 1998; D.M Barch, et al., 1996; Kuperberg, Deckersbach, Holt, Goff, & West, 2007; Lecardeur, et al., 2007). Others use cut-offs based on group means/medians and standard deviations (SD's) (Baving, Wagner, Cohen, & Rockstroh, 2001; Spitzer, et al., 1993) or rely on error data as well as combinations of means and standard deviations (Gouzoulis-Mayfrank, et al., 2003; Kreher, Goff, & Kuperberg, 2009; Ober, Vinogradov, & Shenaut, 1995) still others rely on log transformations (Ober, Vinogradov, & Shenaut, 1997; Surguladze, Rossell, Rabe-Hesketh, & David, 2002). For this thesis, any RT more than 2SD's from the mean of that participant group was replaced with the score equal to 2SD's from the mean.

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1.5 Analogue Models of Psychotic Illness

Schizophrenia analogue models have become increasingly popular over the past few years. These models are an attractive alternative to examining individuals with schizophrenia directly as they have the capacity to control for medication and lifestyle effects related to long term mental illness (Claridge, 1994; Coyle, 1996). There are two models that have become especially popular: the schizotypy and the ketamine analogues. To briefly summarise what will be discussed in detail in the following section; the schizotypy analogue is based on the proposition that psychosis is on a continuum from healthy mental state to severe psychosis. Therefore, healthy participants high on measures of schizotypy are thought to provide a good intermediate measure of psychotic and cognitive symptoms associated without the confounding effects described (Claridge, 1994). The ketamine model is based on the idea that schizophrenia symptoms are related to abnormalities in the glutamate system (Javitt, 2007). While this model is able to control for the confounds of medication and lifestyle effects, it is confounded by the fact that any performance differences identified may be due to ketamine effects and may not be a result of controlling for schizophrenia confounding factors. The strength of the ketamine model lies in the fact that it provides a possible mechanism for the development of psychotic and cognitive symptoms associated with schizophrenia. These models are investigated in the current thesis because both ketamine (Adler et al., 1998; Curran & Morgan, 2000; Morgan et al., 2004; Morgan et al., 2004) and schizotypy models (Johnston et al., 2008; Morgan, Bedford, et al., 2006; Moritz, Andresen, Naber, et al., 1999; Niznikiewicz et al., 2002; Pizzagalli et al., 2001) have both been used previously to model semantic deficits. While these models may provide an important new avenue for understanding semantic deficits in schizophrenia, if we do not understand clearly what aspects of semantic dysfunction they are mimicking then they may simply muddy a body of literature already associated

with high levels of heterogeneity. Therefore, one of the aims of this thesis is to examine these models in detail and determine what aspects of schizophrenia semantic impairment they are best able to mimic so that they may be employed usefully in future research. Chapters Two and Three compare healthy control performance to analogue performance to determine whether these analogues are associated with semantic deficits generally. Chapter Five compares analogue performance to schizophrenia and provides an evaluation of the ability of each analogue to mimic schizophrenia.

1.5.1 Schizotypy

Schizotypy is a continuous personality trait that measures a predisposition to psychosis in the normal population (Claridge, 1994, 1997). This is validated by the finding of genetic (Torgersen, 1994) and prospective studies (Fenton & McGlashan, 1989) , which demonstrate a relationship between schizotypy and schizophrenia. This strategy is thought to more accurately reveal psychopathology underlying schizophrenia by eliminating confounding factors (Claridge, 1994). Cognitive data collected in schizophrenia research is often confounded by variables such as medication (Green & King, 1996) and general intellectual decline (Seidman et al., 2006). Evidence suggests that medications can in some cases improve cognitive performance (neuroleptic treatments) whilst others can cause further impairments (anticholinergics) (Spohn & Strauss, 1989). A meta-analysis examining the effects of traditional neuroleptics including 208 effect sizes from 34 studies concluded that these drugs provide modest to moderate gains in cognitive function (Mishara & Goldberg, 2004). There is also evidence of differences in influence between typical and atypical antipsychotics with atypical associated with greater improvements in cognition with different atypicals improving different areas of cognition (Meltzer & McGurk, 1999). As discussed in section 1.2, there is some evidence that

schizophrenia may be associated with deterioration in intelligence over time (Aylward et al., 1984; Seidman et al., 2006).

Dividing healthy individuals into low and high schizotypy groups provides an experimental design that theoretically provides an analogue to testing schizophrenia patients to healthy controls whilst controlling for these problematic confounds.

There is substantive evidence that schizotypy is related to cognitive abnormalities that mirror those seen in schizophrenia. Evidence exists for difficulties in emotional Stroop priming (Beech, Baylis, Smithson, & Claridge, 1989), ToM/mentalising tasks (Langdon & Coltheart, 1999), sustained attention generally (Lenzenweger, Cornblatt, & Putnick, 1991) which is exaggerated in the disorganisation subtype (Chen et al., 1998). In addition, poor executive function measured as performance on the WCST (Lenzenweger & Korfine, 1994). Especially relevant to the current thesis is the body of evidence implicating similar deficits in priming tasks found in schizophrenia (Johnston et al., 2008; Kiang & Kutas, 2005; Moritz, Andresen, Naber, et al., 1999; Peters, Pickering, & Hemsley, 1994; Pizzagalli et al., 2001).

There is a growing body of evidence suggesting that high schizotypy is associated with abnormal semantic memory. The following is a review of those studies examining explicit semantic function in schizotypy. This is followed by a review of those studies examining implicit semantic priming specifically in schizotypy.

1.5.2 Explicit Semantic Processing in Schizotypy

All the studies examining semantic memory have used the Schizotypal Personality Questionnaire (SPQ) to rate levels of schizotypy in their study samples. The SPQ is made up of 74 questions and 9 subscales. The subscales include: ideas of reference, odd beliefs and magical thinking, excessive social anxiety, odd or eccentric behaviour, unusual perceptual experiences, no close friends, odd speech, constricted affect and suspiciousness. The author of the scale reports high internal reliability (0.90 to 0.91), sampling validity, test-retest reliability (0.82) and convergent validity (0.63) for the scale. He further reports evidence for reliability, convergent validity, and discriminant validity as well (Raine, 1991). These nine separate dimensions are combined to create three factors that correspond conceptually to the well-known reality distortion, disorganization, and negative symptom components identified in schizophrenia.

An ERP study examined the N400 effect in a high schizotypy group (Kiang & Kutas, 2005). The N400 effect has been related to semantic function. Specifically, the N400 amplitude to a target is reduced if it is related to a target. N400 effects are mixed in schizophrenia (Kostova, Passerieux, Laurent, Saint-Georges, & Hardy-Baylé, 2003; Spitzer, 1997; Strandburg et al., 1997) although there does appear to be consistent evidence for N400 abnormalities reflecting abnormal semantic memory. This was one of the reasons for conducting the study in a schizotypy group to eliminate some of the possibly confounding factors. Results showed that there was more activation to unrelated pairs and less activation to related pairs as schizotypy scores increased. This suggests less differentiation in activation to related and unrelated pairs in high schizotypy, similar to schizophrenia performance in so far as abnormalities in semantic processing were detected.

One study (Lenzenweger, Miller, Maher, & Manschreck, 2007) proposed that the speech of individuals scoring high in schizotypy would be associated with more inappropriate semantic intrusions than would their low schizotypy counterparts, similar to schizophrenia (Maher, 2003; Maher, Manschreck, Linnet, & Candela, 2005). Participants were asked to describe a painting known as "The Wedding Feast" and speech transcripts were collected on a minimum of 100 words. When examining the transcripts, the authors found that the disorganisation and reality distortion dimensions and the overall score on the SPQ correlated significantly with more semantic intrusions in speech confirming the schizophrenia finding in schizotypy.

Some authors have suggested that loose semantic associations in schizotypy allow those with high schizotypy to think more flexibly and solve problems more creatively (Karimi, Windmann, Güntürkün, & Abraham, 2007). These authors found that a high schizotypy group were more accurate than the low schizotypy group in solving problems that required creative thinking whilst the two groups did not differ in their abilities to solve analytical problems. The authors argue that this performance reflects a loosening of associations, similar to that found in schizophrenia (Spitzer, Braun, Hermle, & Maher, 1993).

Fisher and colleagues (2007) examined context maintenance using the Deese/Roediger-McDermott (DRM) recognition memory paradigm (Roediger & McDermott, 1995). This paradigm requires participants to remember a list of words designed to prime a critical lure word ('tired', 'pillow' and 'yawn' might be used to prime 'sleep' for example). Intact context maintenance leads to more instances of falsely recognising the lure as having been presented. Authors predicted that context maintenance would be impaired in schizotypy as it is in schizophrenia (Servan-Schreiber D, 1996;

Stratta, Daneluzzo, Bustini, Prosperini, & Rossi, 2000). It was proposed that positive schizotypy would be a significant predictor of poor context maintenance (failure to falsely identify the critical lure word as having been presented in a recognition task). This finding was confirmed suggesting a semantic abnormality similar to that seen in schizophrenia.

Morgan and colleagues (2009) compared a high and low schizotypy group across a range of semantic tasks including a definition task, a naming task, a number of fluency tasks, a semantic categorisation task, a word association task, a synonym identification task and a nonsense sentences task. The two groups differed in only one area, the semantic categorisation task. This task required the groups to determine whether pairs of words belonged to the same category. There were five different types of pairs presented: (1) high frequency (vehicle– bus), (2) low frequency (vehicle–ferry), (3) borderline (vehicle–ski), (4) related but outside the category (vehicle– horse), and (5) unrelated (vehicle– banker). A specific group difference stemmed from the fact that the high schizotypy group made more errors in categorising low frequency pairs correctly. This low frequency deficit effect replicates schizophrenia findings and is suggestive of a semantic storage deficit (Rossell & David, 2006).

Kostova and colleagues (2011) examined semantic function in the left and right hemispheres separately in schizotypy. Schizophrenia findings generally find impaired semantic access in the left hemisphere (Bruder et al., 1999; Løberg, Hugdahl, & Green, 1999) which the authors proposed to replicate in a high schizotypy group. Participants were asked to make semantic judgments on sentences ending with an expected word, or an unexpected word from the same or a different category. They were instructed to press one button if the final word in the sentence was compatible or incompatible

with the rest of the sentence. The high schizotypy group failed to demonstrate a semantic compatibility effect in the left hemisphere (faster RT to confirm an expected sentence ending compared to the RT taken to reject an unexpected ending) in agreement with schizophrenia findings.

1.5.3 Implicit Semantic Priming in Schizotypy

There are a number of significant confounds inherent to schizophrenia semantic priming research. These include some of the same confounds as those reported in any study examining cognition in schizophrenia but with evidence collected that relates specifically to semantic priming. These confounds include the effects of medication, length of illness and slowed processing speed. Medication effects are problematic for priming studies because some medications slow reaction time (Barch et al., 1996) whilst others normalise priming performance thereby confounding results (Goldberg, Dodge, Aloia, Egan, & Weinberger, 2000). Length of illness has a significant and demonstrable effect on priming. Research shows that hyperpriming is associated with the early stages of illness whereas those with a long history of schizophrenia are likely to show the opposite profile characterised by decreased priming (Maher et al., 1996). Finally, schizophrenia is associated with generally slower processing speed; this effects the calculation of priming and gives the false impression of increased priming in this group (Chapman et al., 1994). While these confounds can be reduced in a schizophrenia population, they cannot be eliminated. The schizotypal analogue model of schizophrenia however, provides a method for eliminating these issues.

A number of the following semantic priming papers have used another measure of schizotypy known as the Oxford Liverpool Inventory of Feelings and Experiences O-LIFE scale (Mason, Claridge, & Jackson, 1995). An individual's position on a schizotypy continuum is measured by higher scores on

its four scales and indicates more proneness to psychosis than a normal individual. Four factors are obtained from the O-LIFE: unusual experiences (UNEX), which refers to unusual perception and fantasy thoughts; introvertive anhedonia (INVAN), which measures difficulties in attaining pleasure from social situations, preference for solitude and is related to negative symptoms; impulsive non-conformity (IMPNON), which explores asocial behaviour; and finally, cognitive disorganisation (CogDis), which records aspects of poor attention and concentration. Included in this scale is also the STA, which is a scale designed to reflect the DSM-III-R description of schizotypal personality (Claridge & Broks, 1984) along with a 'Lie' scale and an 'Extraversion' scale. The lie scale was included to detect false responding and the extraversion scale to prevent the scale from seeming too pathological. All scales have alpha coefficients of well over 0.7 with adequate internal consistency.

Pizzagalli and colleagues (2001) used the Magical Ideation Scale (Eckblad & Chapman, 1983) to split their sample into low and high schizotypy. They compared the left and right hemispheres of the two groups in their priming of directly and indirectly related pairs. They authors found that the high schizotypy group showed greater priming for indirect targets compared to the low group in the right hemisphere (Kiefer, Weisbrod, Kern, Maier, & Spitzer, 1998; Weisbrod et al., 1998). This is specific to indirect priming and should not be seen as a contradictory finding to those schizophrenia and schizotypy papers reporting left hemisphere deficits in semantic processing.

Morgan and colleagues (2006) used both short and long SOAs to examine high and low frequency word priming in a high and low schizotypy group, whom were classified using the OLIFE. The authors reported that the low schizotypy group demonstrated more priming at the short than long SOA whilst the high schizotypy group demonstrated increased priming at the long compared to the

short SOA condition. Further, increased priming at the long SOA correlated significantly with both unusual experiences ($r=0.43$, $p=0.03$) and with STA ($r=0.45$, $p=0.02$). There was no frequency effect demonstrated in this study in opposition to the Morgan (2009) categorization study. The authors suggested that this might reflect a slowing in the spreading of activation in the high group or a compensation for abnormal spreading activation that may come into play at the long SOA.

A further priming study (Johnston et al., 2008) examined direct and indirect priming in a high and low schizotypy group. They found that the cognitive disorganization subscale of the O-LIFE correlated positively with indirect priming at a short SOA ($r=0.27$, $p=0.05$). The cognitive disorganization scale is proposed to correspond to thought disorder in schizophrenia. As such, this finding supports the schizophrenia findings that thought disorder is related to greater indirect priming (Pomarol-Clotet, Oh, Laws, & McKenna, 2008).

Another author examined hemispheric priming of ambiguous dominant and subordinate pairs at a short and long SOA (Grimshaw, Bryson, Atchley, & Humphrey, 2010). As discussed in section 1.4.4, an ambiguous dominant pair would be KID-CHILD and an ambiguous subordinate pair would be KID-GOAT. In a healthy group, positive priming is found for dominant pairs whilst negative priming is often elicited in response to subordinate pairs (when the two types of stimuli are presented in the same experiment) (Titone, Levey, & Holzman, 2000). In the low schizotypy group (classified using the Schizotypy Personality Questionnaire), this was the pattern of performance. In the high schizotypy group on the other hand, there was no evidence of inhibition of subordinate meanings supporting the failure to inhibit/greater spread of activation findings in schizophrenia (Spitzer, Braun, Hermle, & Maher, 1993).

The findings from both explicit semantic processing and implicit semantic priming studies support the veracity in using the schizotypy analogue to examine semantic memory deficits in schizophrenia. The current thesis will extend on these findings by examining explicit and implicit semantic processing in the same schizotypy sample and, more importantly, will compare a schizophrenia group to the schizotypy group on these same implicit and explicit tasks.

1.5.4 The Glutamate Model: Ketamine

The dopamine hypothesis is the most widely studied neurochemical hypothesis of schizophrenia. In its simplest form, it proposes that schizophrenia is the result of an excess of dopamine activity in the brain (Davis, 1991). This proposal is based on the observations of the behavioural effects of amphetamines. Amphetamines are a class of drugs that cause excessive dopaminergic stimulation, and are capable of eliciting paranoid psychosis indistinguishable from schizophrenia like paranoia (Javitt, 1991). Further support for this model stems from the high correlation among traditional neuroleptics between the dose found to be effective and the degree to which each drug blocks D2 dopamine receptors. Antipsychotics are in fact effective at doses that occupy around 80% of D2 receptors (Ellison, 1994). Despite its popularity, there are a number of significant weaknesses in this model. For example, a large number of individuals with schizophrenia do not respond adequately to treatment with dopamine antagonists (Davis, 1991). Further, while the dopamine theory has relatively good explanatory power in relation to positive symptoms, it is a relatively poor model for explaining the cognitive deficits and the negative symptoms associated with schizophrenia. Further, there is evidence that amphetamine administration can actually improve negative symptoms, rather than elicit them, in some circumstances (Jentsch, 1999).

The glutamate model provides an alternative, complimentary, neurochemical model of schizophrenia. According to the glutamate model, schizophrenia symptoms may occur as a result of decreased glutamatergic activity in the brain (Javitt, 1991). This model stems from the observation that drugs which affect the glutamate system can cause psychosis. These drugs include PCP and ketamine which affect the glutamate system via their influence on ionotropic NMDA receptors (Javitt, 1991). These drugs are also capable of eliciting psychotic symptoms, including not only the positive symptoms successfully elicited by dopamine agonists, but also cognitive and negative symptoms. The ability of NMDA antagonsists to mimic these additional symptoms makes it a better behavioural model for schizophrenia than the dopamine model. This model is promising enough that researchers have suggested that the evidence gathered so far "make a more compelling case for the role of glutamate/NMDAR in the endophenotype of schizophrenia than dopamine." (Coyle, 2006, pg. 368).

1.5.5 First episode versus chronic schizophrenia

Ketamine, like dopamine, does not provide a perfect model for the symptoms of schizophrenia. For example, clear auditory and visual hallucinations are rare under the influence of ketamine whereas symptoms including visual illusions are more common. Research suggests that these 'dulled' versions of psychotic symptoms are in fact, similar to the pattern of symptoms observed early in the course of schizophrenia (Jentsch & Roth, 1999). As a result, some research even suggests that in the early stages of schizophrenia, there is an excess of glutamate whereas later in the course of the illness, glutamate levels become depleted (Goff, 2001). Further, there is now evidence to suggest that acute ketamine administration may be a better model for early psychosis whilst chronic abusers of ketamine or PCP

demonstrate symptoms more similar to chronic schizophrenia (Jentsch & Roth, 1999; Morgan & Curran, 2006).

Jentsch and Roth (1999) reviewed the small literature available comparing acute administration and chronic use of PCP and ketamine at the behavioural level and made the following observations. Acute administration leads to intense but short lived psychosis whereas chronic administration leads to prolonged psychosis over a period of days to weeks. Psychotic symptomatology after acute administration consists of visual illusions and delusions whereas chronic administration leads to auditory and paranoid hallucinations and largely religious delusions lasting for a longer period (once again, days to weeks). Both acute and chronic administration led to thought disorder although, once again, chronic administration was associated with a longer duration of this symptom (days to weeks). Affect was differentially affected also; acute administration was associated with euphoria and catatonia whilst chronic use was associated with anxious, labile or paranoid feelings. Cognition was transiently affected after acute administration whilst chronic use was associated with persistent deficits. Frontal blood flow was transiently increased after acute administration but was decreased among chronic users. The authors concluded that the acute administration of these drugs did indeed appear to mimic early psychosis better whereas chronic use more closely resembled chronic schizophrenia.

Differences in glutamate metabolism at first episode versus chronic schizophrenia have also been identified using proton magnetic resonance spectroscopy (1H-MRS). This method of study allows *in vivo* quantification of glutamatergic metabolite levels in schizophrenia. These studies, on drug naïve first episode patients, have demonstrated increased glutamine levels in the left anterior cingulate and the thalamus in never treated individuals with first-episode psychosis and decreased

levels of both glutamate and glutamine in the left anterior cingulate in individuals with chronic schizophrenia (Bartha et al., 1997; Theberge et al., 2007). It is important when reading such studies to examine length of illness. Although none of the studies in this area specify what qualifies as early versus chronic schizophrenia, it appears that 'first episode' is the criteria required for 'early psychosis'. While this seems quite acceptable, it is also important to determine whether the diagnosis of schizophrenia is appropriate. After all, early psychosis does not equal early schizophrenia. It may evolve into bipolar disorder, may be drug induced and temporary, or may remit altogether. As such, it would seem appropriate that a higher level of certainty about the etiology of the disorder would require that DSM criteria for schizophrenia and not simply schizophreniform disorder are met. This means that participants should be in their first episode of psychosis, but should have had continuous symptoms lasting at least 6 months. The schizophrenia participants in Bartha's study definitely meet DSM criteria for schizophrenia from a length of illness point of view. It is not as clear with the Theberge study with illness length reported as 21 months with a standard deviation of 24 months. More recently, Olbrich et al. (2007) used absolute-quantification short-echo magnetic resonance spectroscopy (MRS) to examine glutamate levels in first episode schizophrenia (first episode was reported to satisfy DSM criteria). They also found evidence for increased glutamate in a first episode schizophrenia group in comparison to a matched healthy control group. This time, the increase was in the dorsolateral prefrontal cortex. Higher levels of glutamate were also found in the hippocampus however, this result neared, but did not reach, significance. It is important to point out however, that not all members of the schizophrenia group had increased glutamate levels. Authors contend that increased glutamate at disease onset may represent a specific endophenotype of schizophrenia.

Another study found that a high risk group (individuals with a parent who was diagnosed with schizophrenia) demonstrated higher levels of glutamate in the medial frontal cortex (Tibbo, 2004).

Further research examined CSF levels of glutamate in first episode individuals with schizophrenia (it is unclear whether DSM criteria for schizophrenia were met) (Hashimoto et al., 2005). The first episode group was drug naïve and matched with a healthy control group. Lumbar puncture was used to collect CSF samples. Results showed that the ratio of glutamate and glutamine were higher in the CSF of the first episode group in comparison to the controls. There is, of course, also evidence that glutamate levels are depleted, even in the early stages of the illness (Palomino et al., 2007). This research group took whole blood samples from first episode schizophrenia and bipolar patients on first admission, and again one, six and twelve months following the initial admission. The fact that participants continued to meet diagnosis for schizophrenia at follow up suggests DSM criteria for schizophrenia were met. Results showed that glutamate levels were significantly reduced in all psychosis groups regardless of whether or not they went on to receive a diagnosis of bipolar disorder or schizophrenia. Glutamate levels increased into the normal range by the six month mark which researchers attributed to the action of antipsychotic medication. It is important to point out that this study used whole bloods which are a less accurate measure of glutamate levels in the brain than the CSF examination method used by Hashimoto et al. (2005). This may account for differences between the studies although differences in participants psychosis may also be an issue given that details of illness are not provided in the Hashimoto study.

In the postmortem studies discussed below; authors find evidence of reduced glutamate activity in the brains of individuals diagnosed with schizophrenia. A closer examination of the demographics

of these participants demonstrates why this is not contradictory to the notion that early in the illness, increased glutamate is the norm. In one study (Ibrahim, 2000), all 12 schizophrenia brains came from individuals between the ages of 61 and 86; all of whom had demonstrated schizophrenia symptoms from before the age of 40, so at least 20 years of illness. In the other study (Gao, 2000) the mean age of the 31 individuals at time of death was 43.2 years suggesting that they were not early in the course of their illness either. As such, it is likely that these results reflect the effects of chronic schizophrenia.

With regard to results of NMDA agonists (also discussed below), there is one piece of research which suggests that NMDA agonists reduce symptoms in a prodromal psychosis group specifically (Woods, Walsh, Pearlson & McGlashan, 2006). Ten participants were included in this study and seven completed. Participants were given a dose of 0.4g/kg of glycine twice a day (comparable to other studies in the area (Javitt, 2007) for 8 weeks and were followed up for 16 weeks following discontinuation of the drug. None of the seven participants who completed the study became psychotic during the follow up period and all seven demonstrated significant improvement on a prodromal symptom scale over the 8 weeks. Authors concluded that this was evidence that NMDA agonists could produce therapeutic changes when used alone in the prodromal or early phases of psychosis. There are a number of shortcomings associated with this study. Sample size was very small with only seven participants completing and follow up time was also short at only four months. No details about length of illness are provided and, in addition, no comparable control group was included. Researchers did not collect data (CSF or even full bloods) to estimate glutamate levels prior to the introduction of glycine. Finally, one of the three participants who withdrew did so because of lack of efficacy, something which the authors did not follow up or attempt to explain.

At this stage, the evidence for hyperglutamatergic function in prodromal/first episode individuals is reasonably strong and there are few studies available that have systematically attempted to disprove this hypothesis. This does not mean, however, that all early psychosis individuals have hyperglutamatergic function. Like most areas of schizophrenia research, it is more likely that this hypothesis accounts for a subgroup of individuals. Further research comparing first episode and chronic schizophrenia groups is necessary. Even more useful would be a longitudinal study spanning years, as opposed to months, to determine the pattern of change in glutamate levels. Correlating the changes in glutamate with positive, negative and cognitive symptoms is also a necessary addition. Determining whether a family predisposition to schizophrenia has any effect on the levels/changes in glutamate over time also needs to be considered.

1.5.6 Glutamate is everywhere

Initially, there was some scepticism regarding the validity of the glutamate model of schizophrenia stemming from the fact that glutamate is the most common excitatory neurotransmitter in the brain. In fact, approximately 60% of neurons utilise glutamate as their primary neurotransmitter up to 2/3 of brain energy metabolism is related to reuptake and recycling of glutamate (Goff & Coyle, 2001). It was therefore deemed unlikely that a model suggesting generalised abnormalities in glutamate activity would be able to account for the very specific clinical characteristics of schizophrenia.

However, this model has become more refined based on research examining NMDA antagonists, postmortem and genetic studies. These investigations suggest that deficits in specific

glutamate receptors or glutamate deficits in specific brain regions may account for the specific symptoms of schizophrenia. These studies are examined next.

Because the glutamate system has a number of different receptor families, configurations, transmitters/modulators, and modulating receptor sites, the task of uncovering a pathologic site involving glutamate is complicated. Figure 1 below describes a simplified version of the breakdown of the glutamate system including examples of glutamate agonist's and the receptors they affect. It is included not only to illustrate the large number of possible points of deficit; it can also be referred to when reading about the postmortem, genetic and NMDA antagonists studies examined next.

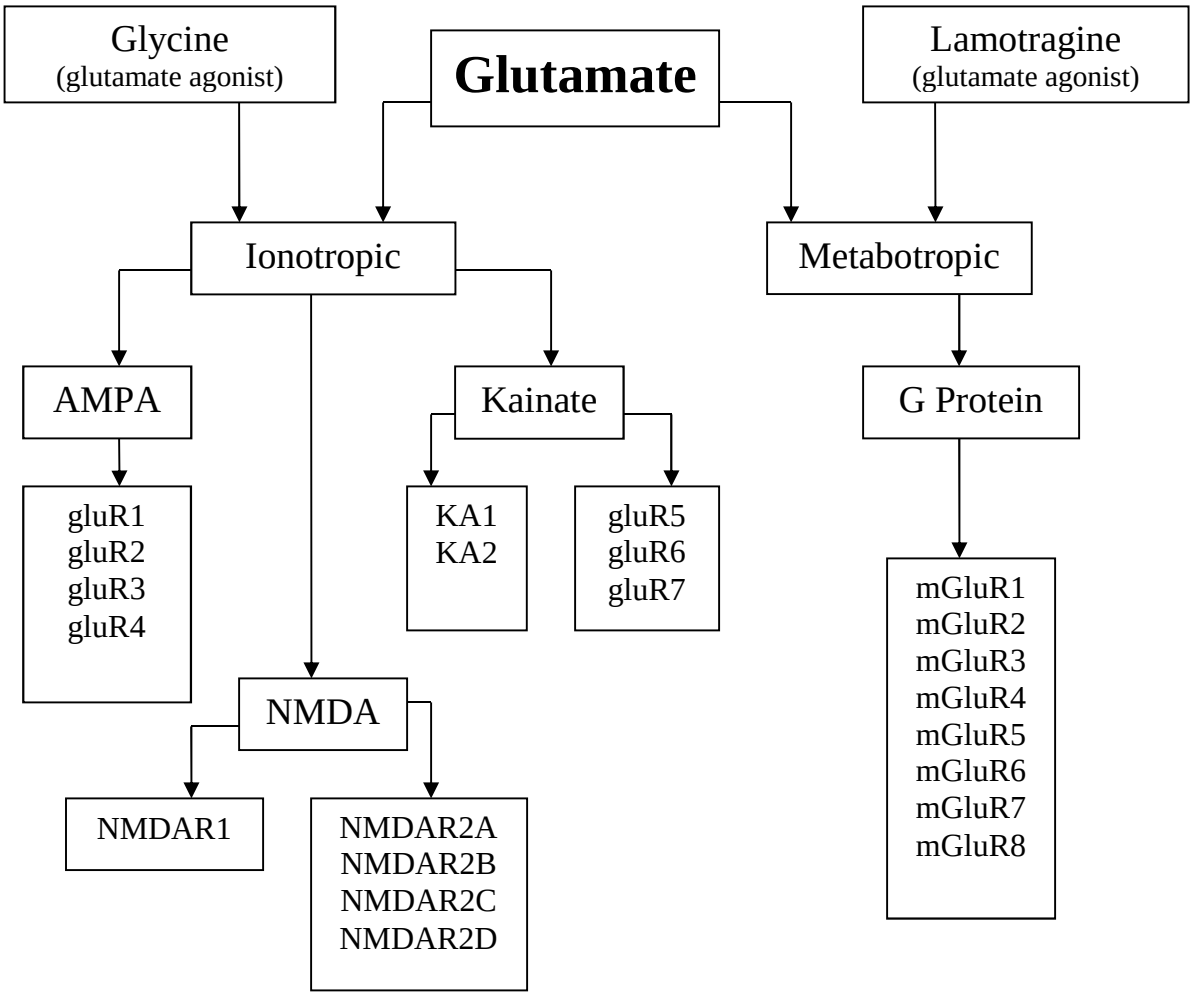

Figure 1.6 Glutamate Receptors

1.5.7 Postmortem studies

Researchers have used postmortem studies to examine glutamate function in schizophrenia. One study (Ibrahim, Hogg, Healy, Haroutunian, Davis & Meador-Woodruff, 2000) compared the number of glutamate receptors in the thalamus of individuals with and without a diagnosis of schizophrenia. Authors found that, in the schizophrenia group, there were significantly lower levels of thalamic glutamate receptor expression in certain nuclei and in certain subunits of glutamate receptors

including NMDAR1, NMDAR2B, NMDAR2C, gluR1, gluR3 and KA2. These differences were most prominent in nuclei with reciprocal projections to the limbic system. Authors concluded that this might cause hypoglutamatergic activity in the thalamus among people with schizophrenia. Another study examined glutamate receptors in the hippocampus of 31 individuals who had been diagnosed with schizophrenia (Gao, 2000) they found a slight, but significant, reduction in AMPA receptor binding and a reduction in the level of mRNA for NMDAR1. Authors concluded that the reduction in NMDAR1 specifically might lead to reduced glutamatergic transmission from the hippocampus which might, in turn, underlie the hypoglutamatergic state in regions of the limbic system noted in the study by Ibrahim et al. (2000).

1.5.8 Genetic Studies

In their review of studies in search of genetic markers for schizophrenia, Harrison and Weinberger (2005) identified seven genes which may be linked to the development of this disorder (COMT, Dysbindin, Neuregulin, regulator of G-protein Signaling 4, Disrupted In Schizophrenia 1, metabotropic glutamate receptor-3, G-72, D-Amino acid oxidase and praline oxidase). They implicated dopamine function but, in addition, pointed out that NMDA receptor-mediated glutamate transmission is “especially implicated” (Harrison & Weinberger, 2005, pg.40). Coyle (2006) examined the genes implicated as being involved in glutamate function (G-72, metabotropic glutamate receptor 3, Dysbindin and NRG1) and described how abnormalities in these genes could lead to a down regulation of glutamate within the brain.

1.5.9 NMDA Receptor Glycine-Site Agonist Studies

Based on the evidence for glutamatergic abnormalities in schizophrenia, attempts have been made to correct such imbalances using drugs that work on the glutamate system. This is not a straight forward process; for example, it is not safe to increase glutamate levels in the brain as it can lead to seizures and excitotoxicity (Javitt, 2007). Instead, drugs which increase the efficacy of glutamate already present are being explored; the most popular drug being Glycine, an NMDA agonist. Early trials of Glycine were not successful due to the low doses used (5-15g/day) and because Glycine does not cross the blood brain barrier well (Goff & Coyle, 2001). More recent studies have increased the dose of Glycine. A review of 11 such studies has been conducted by Javitt (2007). All studies included individuals with a diagnosis of schizophrenia who took Glycine or D-Serine (both full agonists) as an adjunct to their normal antipsychotic medication. All eleven studies demonstrated large effect sizes with improvements in both negative and cognitive symptoms. In some, but not all Glycine studies, improvement correlated with baseline Glycine levels with participants with lower baseline levels demonstrating the greatest improvements. Research suggests that partial agonists like D-cycloserine is not as effective in reducing symptoms and, in addition, has a smaller therapeutic window with higher doses associated with exacerbation of symptoms.

While information regarding the symptoms elicited by ketamine will be collected, for this thesis, the ability of ketamine to induce deficits in semantic memory is of primary importance. Semantic memory is discussed next.

CHAPTER 2. KETAMINE: IMPLICIT AND EXPLICIT SEMANTIC MEMORY

DECLARATION FOR THESIS CHAPTER 2

Declaration by candidate:
In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, co-ordination of co-authors, data collection, data analysis and writing of manuscript.	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Susan Rossell	Supervisor of Erica Neill's PhD. Responsible for study design. Provided assistance in data analysis and proof reading of the manuscript
Sarah McDonald	Research nurse whom supervised the administration of ketamine, responsible for random allocation of participants to treatment condition (other authors were blind). Provided follow up care to participants.
Nicole Joshua	Research assistant responsible for the creation of computer tasks. Also responsible for training Erica Neill in task administration.
Celia J. Morgan	Assisted in the design of the study. Provided on going assistance with data analysis and proof reading of the manuscript.
Nicholas Jansen	Anaesthetist providing supervision of ketamine administration.

Candidates Signature:  **Date:** 12/10/12

Declaration by co-authors
The undersigned hereby certify that:
(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from December 2008

Celia J. Morgan Signature:  **Date:** 12/10/12

Declaration by candidate:

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, co-ordination of co-authors, data collection, data analysis and writing of manuscript.	70%

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Celia J. Morgan	Assisted in the design of the study. Provided on going assistance with data analysis and proof reading of the manuscript.
Nicholas Jansen	Anaesthetist providing supervision of ketamine administration.

Candidates Signature: [redacted] **Date:** 12/10/12

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship. They have participated in the execution of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from December 2008

Nicole Joshua (Knott) Signature: [redacted] **Date:** 12/10/12

Declaration by candidate:

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

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Selection of behavioural tasks, co-ordination of co-authors, data collection, data analysis and writing of manuscript.	70%

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Nicholas Jansen	Anaesthetist providing supervision of ketamine administration.

Candidates Signature: [redacted] **Date: 10/10/12**

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(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
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Sarah McDonald Signature: [redacted] **Date: 10/10/12**

Declaration by candidate:

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, co-ordination of co-authors, data collection, data analysis and writing of manuscript.	70%

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Candidates Signature: [redacted] **Date: 10/10/12**

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Susan Rossell Signature: [redacted] **Date: 10/10/12**

Declaration by candidate:

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

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(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from December 2008

Nicholas Jansen Signature: SIGNATURE NOT AVAILABLE

2.1 Chapter Guide

This is the first of four chapters investigating implicit and explicit semantic function in schizophrenia. It Chapter investigates one analogue model for schizophrenia function: The ketamine model.

This chapter includes the article entitled *Using Ketamine to Model Semantic Deficits in Schizophrenia* which can be found in Appendix B. It also includes additional information to that contained in the article. Sections 2.4.3 provides greater detail outlining the logic behind the ketamine dose chosen for the study. Table 2.1 provides a summary of the psychotic symptoms that have been elicited by previous ketamine studies. Table 2.2 provides a summary of the effects of ketamine on semantic function. Section 2.4.4.1 provides further information regarding the post testing session and 2.4.5 provides additional information about the measures employed for the study. Finally, section 2.4.6.1 explains why masked priming was not employed to examine implicit priming.

2.2 Abstract

Semantic deficits constitute a core cognitive abnormality in schizophrenia. In the current study the N-methyl-D-aspartate receptor antagonist ketamine was administered to healthy individuals acutely whilst they performed semantic processing tasks that included word pairs of differing degrees of semantic relatedness. Two dimensions of semantic processing were investigated: 1) explicit versus implicit processing, that is, unconscious versus concscious processing of semantic relationships and 2) direct versus indirect processing, that is words pairs that are closely (LION-TIGER) or distantly (LION -STRIPES) related. The acute effects of ketamine (0.8mg /kg/hr over 80 minutes with approximate target plasma levels of 200ng/ml) were examined in a placebo-controlled double-blind repeated measures group design with 19 participants. It was predicted that ketamine would disrupt access to semantic memory as evidenced in schizophrenia, especially the indirectly related word pairs. In addition, implicit and explicit processing were predicted to be differentially affected. Ketamine administration did result in abnormal performance in the reaction time responses to implicitly presented indirectly related word pairs (that is, greater priming), and reduced accuracy for explicit pairs. Performance on the directly related word pair tasks (both implicit and explicit) were similar across ketamine and placebo conditions, except for the suggestion of abnormal semantic matching in the accuracy data in the implicit task. The study confirms implicit indirect semantic processing is changed under the influences of ketamine akin to schizophrenia. Future research comparing a schizophrenia and ketamine group directly on these tasks is needed to determine the similarity of impairments.

2.3 Introduction

The glutamate model provides a complementary alternative, to the dominant dopamine model of schizophrenia. Ketamine, which affects the glutamate system, can induce a transient psychosis via its influence on ionotropic N-methyl-D-aspartate (NMDA) receptors (Javitt, Zukin, Heresco-Levy, & Umbricht, 2012; Javitt, 1991). Unlike dopamine agonists, ketamine is capable of eliciting not only positive symptoms, but the cognitive and negative symptoms as well. This model is promising enough that researchers have suggested that the evidence gathered so far "make a more compelling case for the role of glutamate/NMDA in the endophenotype of schizophrenia than dopamine." (Coyle, 1996, p. 368).

There is a growing body of research examining ketamine's effect on cognition with authors comparing patterns of impairment on cognitive tasks to those seen in schizophrenia. Similar deficits in executive functioning (Adler et al., 1998; Krystal et al., 1994; Krystal et al., 1995), facial emotion processing (Abel et al., 2003), and long term memory (both episodic and semantic memory) have been found. Acute administrations of ketamine induced impairments in episodic memory characterised by greater impairment in learning and recall than recognition (Krystal et al., 1994; Krystal et al., 1995; Malhotra et al., 1997; Malhotra et al., 1996; Newcomer et al., 1999), a pattern similar to that seen in schizophrenia (Aleman, Hijman, de Haan, & Kahn, 1999). There is also a growing body of literature examining semantic memory deficits under the influence of ketamine (Adler et al., 1998; Curran & Morgan, 2000; Morgan et al., 2004; Morgan et al., 2004; Morgan, Rossell, et al., 2006). This is particularly noteworthy because, while many drugs are capable of impairing episodic memory, semantic memory is generally more difficult to disrupt (Tulving, 1972). In addition, semantic memory has not received the same attention in the schizophrenia literature as episodic memory despite evidence

indicating the deficits in this system are comparable to those seen in individuals with mild-to-moderate Alzheimer's disease (McKay et al., 1996).

A majority of studies examining the impact of ketamine on semantic memory have relied on verbal fluency tasks (Adler et al., 1998; Curran & Morgan, 2000; Morgan et al., 2004; Nagels, Kirner-Veselinovic, Krach, & Kircher, 2011) with three of these studies (one examining acute administration and one chronic abuse) (Adler et al., 1998; Curran & Morgan, 2000; Nagels et al., 2011) finding that, like schizophrenia, ketamine impairs verbal generation. Other research using a sentence completion task found that ketamine slowed reaction time (Morgan et al., 2004; Morgan, Rossell, et al., 2006). Unfortunately, verbal fluency tasks are confounded by executive elements and response on the sentence completion task could be attributed to slow processing speed. This data is therefore inconclusive; the current study offers a unique extension to the literature by including a number of exclusively semantic tasks. Semantic memory is an area of particular interest in schizophrenia research because evidence suggests that particular symptoms arise, or are exacerbated, as a result of deficits in this memory system. These include thought disorder (TD) (Leeson, McKenna, Murray, Kondel, & Laws, 2005; Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007; Vassallo, Crow, & Leinonan, 1998), and the formation and maintenance of delusions (McKenna, 1991; Rossell, 1999; Rossell et al., 1999). Some studies have reported levels and patterns of TD after ketamine administration that are similar to those seen in schizophrenia (Adler et al., 1999). Others have noted significant differences in the nature of speech elicited by ketamine specifically, ketamine induced TD was characterised by reduced idea density compared to a matched schizophrenia group (Covington et al., 2007; Covington et al., 2009). Still others have reported only very low levels of TD after ketamine administration (Pomarol-Clotet et al., 2006). Studies have noted that ketamine can also elicit delusional thinking (Pomarol-Clotet et al.,

2006) although direct comparisons between the nature of the ketamine delusions and those seen in schizophrenia have not been made.

The semantic priming task has been widely used to understand not only the structure of semantic memory but also how it is accessed. This task has been especially well used by researchers investigating schizophrenia to understand deficits in this system. Semantic priming refers to the finding that participants respond more quickly to a word if it is preceded by a related word than if it is preceded by an unrelated word. The literature on semantic priming in schizophrenia is conflicting with some research finding normal priming results, some finding increased priming and others, decreased priming (Minzenberg et al., 2002; Pomarol-Clotet et al., 2008). Despite these conflicts, a recent review and a meta-analysis have agreed that indirectly related word pairs (LEMON-SWEET) elicit increased priming in schizophrenia (Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007). This finding has been interpreted in a number of ways, but the dominant interpretation is that over activation or a lack of inhibition in this system can lead to the intrusion of unrelated, or distantly related words, into thought and speech (Spitzer, Braun, Hermle, & Maier, 1993). There have been two ketamine semantic priming studies (Morgan, Rossell, et al., 2006; Stefanovic et al., 2009). Both studies demonstrate that ketamine administration results in abnormalities in strategic priming. Only one study has examined indirect relationships under ketamine and they found impairment under strategic but not unconscious processing. The current study improves and extends on this study by examining the unconscious and strategic divide and, in addition, implicit and explicit access to semantic memory.

To understand the pattern of memory deficits seen in schizophrenia, and as a result of ketamine administration, it is useful to be more specific than simply identifying a general deficit in memory.

Like the earlier work of Kuperberg and colleagues (Kreher et al., 2009; Kuperberg et al., 2008) implicit and explicit access to semantic memory are examined separately in this study. Implicit retrieval occurs outside conscious awareness whilst explicit retrieval requires conscious, effortful awareness for retrieval (Horan et al., 2008). Generally speaking, research finds that implicit episodic retrieval (word stem completion) is intact in schizophrenia (not to be confused with implicit learning) (Bazin & Perruchet, 1996; Clare et al., 1993; Danion, Meulemans, Kauffmann-Muller, & Vermaat, 2001), whereas explicit episodic memory is impaired (Clare et al., 1993). It is significant that semantic priming, an implicit semantic task, is associated with abnormalities in schizophrenia (Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007) suggesting that the nature of memory impairments in schizophrenia are not uniform across long-term memory stores.

In the current project we sought to understand the nature of semantic memory deficits elicited by ketamine, by dissecting whether deficits are present at both an implicit and explicit level; further whether deficits are more or less pronounced with indirectly related word pairs compared to direct. Participants were given a test battery of four tasks that examined implicit and explicit access to semantic memory using both direct and indirectly related word pairs; once after the administration of ketamine and once after placebo. For task one (implicit indirect) it was hypothesised that under the influence of ketamine, participants will demonstrate abnormal indirect priming (Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007). For task two (implicit direct), given the heterogeneity of priming results using directly related word pairs, no specific hypothesis with regard to ketamine performance were made. For task three (explicit indirect), the Object Task created by Kraut (2002) was used to examine explicit access to indirect associations. This task has been used in a number of experiments examining schizophrenia (Assaf et al., 2007; Kraut, Calhoun, Pitcock, Cusick, & Hart, 2003; Kraut,

Kremen, et al., 2002). Assaf (2007) reported on behavioural data and found that their schizophrenia group showed a trend toward categorising unrelated pairs as related (error data) and were slower to categorise related pairs correctly. Given the indirect priming results and those reported by Assaf it was hypothesised that ketamine will cause abnormalities on the Object Task. For task four (explicit direct), a basic Association Task was used as a measure of explicit, direct access to semantic memory and requires participants to determine whether pairs are related (CAT-DOG) or not (CAT-PENCIL). This exact task has not been used in the schizophrenia literature but it is necessary to have an explicit version of the direct priming task. We predicted that in comparison to the explicit indirect task (Object Task) performance would be better on the explicit direct task (Association) during ketamine given the simple and highly structured nature of this task. If the pattern of deficits were as predicted we will have confirmed that ketamine administration results in error and RT impairments (a) to both implicit and explicit processes in semantic memory; and (b) that impairments are restricted to indirectly related material. Finally, given that there is evidence that semantic abnormalities are associated with the presence of thought disorder and delusions (Leeson et al., 2005; McKenna, 1991; Pomarol-Clotet et al., 2008; Rossell et al., 1999; Rossell & Stefanovic, 2007; Vassallo et al., 1998), it was hypothesised that tasks which elicit semantic abnormalities under ketamine would correlate positively with the presence of these symptoms.

2.4 Methods

This is a double-blind, placebo-controlled, repeated measures design.

2.4.1 Participants

Participants included 22 healthy individuals aged between 18-35 years. Nineteen full sets of data were included in the final analysis. Recruitment and ethical approval were obtained through the University of Melbourne.

2.4.2 Testing and Materials

2.3.2.1 Screening

Demographic information and a health questionnaire were completed in screening. Eligibility criteria required participants to be aged between 18 and 35 and have English as a first language. Exclusion criteria included: A personal or family history of psychotic disorders, a substance misuse disorder at time of testing or a head injury involving a loss of consciousness longer than 5 minutes. Because ketamine is used as an anaesthetic, a number of anaesthesia screening questions were also used for screening purposes. Participants were given a medical check-up to ensure that weight, blood pressure and blood oxygen saturation were all within normal range (persons were excluded if they had high blood pressure > 140/90 [Heart Foundation of Australia cut off for high blood pressure]). As a part of the screening process, participants filled out the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991) designed to measure all nine traits associated with Schizotypal personality disorder as outlined in the DSM-III-R. The SPQ was used in the current study to exclude any individuals whose scores were high enough to suggest the presence of schizotypal personality (that is scores > 48.9). All participants gave witnessed written informed consent in accordance with the Declaration of Helsinki.

2.4.3 Ketamine Dosing

Determining the correct dose of ketamine for administration began with a review of the literature examining the effect of ketamine on the manifestation of psychotic symptoms (Table 2.1). The first issue that arose was the difference in reporting of ketamine levels. Some authors report the dose administered (in mg/ml or mg/kg) whilst others described the steady state venous plasma levels of ketamine detected (ng/ml). There is also variation in the amount of ketamine used across studies even when the method of reporting dosing was the same. Further, in some studies, a bolus was administered before steady state infusion to quickly increase ketamine levels whilst in other studies, this method was not used. The one clear message from the review was that doses needed to be above those reported by Oranje et al. (2000) to achieve detectable behavioural effects, but not much higher than those reported by Pomarol-Clotet et al. (2006) or Morgan (2006) to avoid nausea.

Table 2.1 *Effects of Ketamine Dose on Schizophrenia Symptoms*

Author	Dose of Ketamine		Participant Responses
(Krystal et al., 1994)	0.1mg/kg or 0.5 mg/kg over 40 minutes	N=19	No behavioural effects of low dose, high dose group endorsed both positive and negative symptoms, dissociation and suspiciousness
(Malhotra et al., 1996)	0.12mg/kg bolus, 0.65mg/kg over an hour	N=15	Ketamine increased TD, withdrawal/retardation but not hostility
(Breier, Malhotra, Pinals, Weisenfeld, & Pickar, 1997)	0.12mg/kg bolus, 0.65mg/kg infusion over 1 hour	N=17	Conceptual disorganisation, unusual thought content, hallucinatory behaviour, no significant suspicion or anxiety/depression
(Adler et al., 1998)	0.12mg/kg bolus 0.65mg/kg over 90 minutes	N=10	Increases in thought disorder
(Newcomer et al., 1999)	Loading doses: 0.27mg/kg, 0.081mg/kg, and 0.0243mg/kg, = 150 ng/ml; 45 ng/ml; 13.5 ng/ml	N=15	Ketamine, under these dosing conditions, produced mild dose-dependent positive and negative schizophrenia- like symptoms.
(Oranje et al., 2000)	0.3mg/kg first 40min, 0.0495 mg/kg next 10min, 0.213 mg/kg last 85min	N=18	No significant difference could be detected between the placebo and ketamine condition at a behavioral level
(Lahti, Weiler, Michaelidis, Parwani, & Tamminga, 2001)	0.1, 0.3, 0.5mg/kg bolus over 60 seconds	N=18	Scores on BPRS total, psychosis and withdrawal were significantly increased by ketamine
(Abel et al., 2003)	0.23mg/kg bolus, 0.5mg/kg infusion over 1 hour.	N=8	Increases in depersonalisation, dissociation, thought disorder, withdrawal, and hostility (without incident)
(Morgan et al., 2004)	0.4 or 0.8mg/kg bolus over 80 min	N=18	There was a trend for the 0.4-mg kg ketamine group to like the effects of the drug more than the 0.8-mg kg
(Morgan, Rossell, et al., 2006)	100ng/ml or 200ng/ml over 1 hour	N=48	Increased dissociation and schizotypal symptoms. One participant dropped out of high dose group due to distress
(Pomarol-Clotet et al., 2006)	1mg/ml bolus, then 200ng/ml over unknown time period	N=15	Feeling unwell, poor concentration, tiredness and nervous tension, heightened perception of colour and sound, and visual illusions. Abnormal temporal and touch perception, and delusional thought

(Stefanovic et al., 2009)	75ng/ml or 150ng/ml over 2 hours	N=48	Increased positive, negative and anxious symptoms (BPRS). Increased schizotypy symptoms in total (PSI).

Following this review, a review was undertaken of the doses used in studies examining semantic memory function specifically (Table 2.2). [1] Only one ketamine study examining semantic priming specifically had been published at the time when dosing levels were being determined (Morgan, Rossell, et al., 2006). Authors found that ketamine did disrupt semantic priming with the most dramatic disruption seen at the higher dose (200ng/ml). It is not possible to translate the blood levels back to dosage in an exact way. Instead, after discussion with both Celia Morgan, who had conducted studies reporting both the blood levels (2006) and the dosage levels (2004) and with the anaesthetist Nicholas Jansen involved in the study, it was determined that a bolus of 0.12mg/kg and an ongoing infusion of 0.8mg/kg would be somewhere in the area of the 200ng/ml dose used by Morgan. The agreed upon dose was at the higher end of ketamine dosing associated with some nausea (Pomarol-Clotet et al., 2006) and increased risk of participant drop out (Morgan, Rossell, et al., 2006). Given the demonstrated effects on priming of ketamine at these levels, it was determined that this was an appropriate dose for investigating semantic priming deficits.

[1] Studies examining ketamine users exclusively were not included in Table 2.1 as they did not provide an indication of the relationship between dose and psychosis. They were included in Table 2.2 as they indicate the potential for ketamine to impair semantic function specifically.

Table 2.2 *Effects of Ketamine Dose on Semantic Function*

Author (Year)	Ketamine Dose	Task Used	Participants	Findings
(Krystal et al., 1994)	0.1mg/kg or 0.5 mg/kg over 40 minutes	Verbal fluency	19 healthy participants	Impaired fluency
(Adler et al., 1998)	0.12mg/kg bolus 0.65mg/kg over 90 minutes	Semantic and Phonological Fluency	10 healthy participants	Semantic impairment
(Curran & Morgan, 2000)	Varied (ketamine users)	Semantic Fluency and Speed of Comprehension	20 ketamine users 19 controls	Semantic impairment
(Curran & Monaghan, 2001)	Varied (ketamine users)	Semantic and Phonological Fluency	19 infrequent ketamine users, 8 frequent users	Semantic retrieval deficit
(Morgan et al., 2004)	0.4 or 0.8mg/kg bolus. Tested for 80 minutes	Semantic and Phonological Fluency and Speed of Comprehension	54 healthy participants	Slowed semantic processing
(Morgan, Monaghan, & Curran, 2005)	Varied (ketamine users)	Speed of Comprehension and Semantic Fluency	18 ketamine and 10 polydrug users tested twice over a 5 year period	Semantic memory improved as ketamine decreased
(Morgan, Rossell, et al., 2006)	100 or 200ng/ml infused over 60 minutes	Semantic Priming	48 healthy participants	Impaired semantic access: long SOA
(Stefanovic et al., 2009)	75 or 150ng/ml over 2 hours	Semantic priming	48 healthy participants	Impaired long SOA only

2.4.4 Testing Sessions

Participants attended two 120 minute testing sessions which were separated by between one and two weeks (mean number of days =9.79, SD=6.06). In one of the two sessions, participants were

intravenously administered ketamine and in the other, a placebo, which consisted of a saline solution (0.9% NaCl solution). Order of substance administration was randomised across the two sessions. Only the anaesthetic team knew the order of administration. Both the research psychologist administering the clinical and cognitive battery and the participant were blind to condition. For safety reasons, participants were required to fast for six hours prior to each session. Participants were cannulated using a 20g sharp needle in the end of a 20mL syringe. A bolus of 0.12mg/kg was administered to rapidly raise the level of ketamine in the blood. This bolus was followed by a steady infusion of 0.8mg/kg/hour of ketamine over an 80-minute period. The program uses a bolus elimination-transfer infusion scheme based on the Clements pharmacokinetic model (Clements, Nimmo, & Grant, 1982). A steady state of predicted plasma ketamine/placebo concentration according to the model was achieved in a period of 10 minutes. Ketamine levels were maintained by continuous administration during the testing. Testing began 10 minutes after bolus administration. In all cases, participants reported feeling significantly affected within 10 minutes of the ketamine bolus being administered. Blood pressure, heart rate and blood oxygen saturation levels were checked every twenty minutes throughout the testing period. One participant's testing session was terminated due to extreme nausea. Another could not be catheterised at time two. Finally, a third was familiar with semantic tasks and so did not complete those parts of the testing battery. The pilot participant had plasma levels taken 40 minutes after the infusion started to confirm plasma levels of 200ng/ml were reached (confirmed in our analysis). These levels are similar to another ketamine study that examined semantic priming (Morgan, Rossell, et al., 2006). Plasma levels were only taken from the pilot participant due to budget limitations.

2.4.4.1 Post Testing Session

After behavioural testing, participants were provided with light refreshments. Participants remained in the care of the researcher and the anaesthetist nurse until they were judged to be street ready. Participants were provided with the telephone number of the researcher to use in the unlikely event of persisting disturbances. Participants were also asked if they consented to be contacted a week following the experiment, and six months later to undergo a brief questionnaire to confirm there were no persisting effects. They were also instructed not to drive, operate machinery, engage in hazardous activities, drink alcohol or take any other recreational drugs for 24 hours following the experiment.

2.4.5 Clinical Measures

Prior to each session, the 18-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) was administered to determine that participants were not currently experiencing any symptoms of anxiety, depression or psychosis. This scale was designed to evaluate the psychiatric status of an individual. It can be administered rapidly and can be used to monitor changes. In the current study, this scale was used in the screening session to determine the presence of any unreported mental illness. It was used again at the beginning of each testing session to look for any changes in mental health during participation in this project. An examination of the BPRS scale showed that it has good validity and reliability (Hafkenschied, 1991). Inter-rater reliability was found to be poor in this study. Given that only one rater conducted the interview in this study, this is not a significant problem.

The Clinician Administered Dissociative States Scale (CADSS) (Bremner, Mazure & Putnam, 1998) was administered in the middle of each session to determine the level of dissociative symptoms experienced by participants. This scale was developed to measure the presence of current dissociative

symptoms including gaps in memory not due to ordinary forgetting (amnesia), seeing things in black and white (derealisation), distortions of the sense of one's own body, out of body experiences (depersonalisation), distortions in visual perception, (seeing things as if they are in a tunnel) and fragmentation of the sense of the self (identity disturbance) (Bremner, Mazure & Putnam, 1998). This was administered to participants in both testing sessions to determine whether dissociative symptoms were more prominent under the influence of ketamine, and if present, which symptoms were most often endorsed. While traditionally the CADSS is half interview and half self-report, for this study, the CADSS was administered as an interview so that ratings of thought disorder (from the Thought, Language and Communication Scale, discussed below) could be taken from responses.

The Schizotypal Symptomatology Scale (SSS) is a self-report scale that collects information about psychotic like symptoms (Curran & Morgan, 2000). By adding together the items that specifically addressed delusional thinking, a delusion measure was created (items 4,7,11,14,17,19,25,40,42 and 48 were included in this subscale). This was given to participants after the infusion so they could rate the symptoms they experienced during testing.

The Thought Language and Communication scale (Andreasen 1978) was administered to record levels of thought disorder (TD) among participants. There are numerous scales designed to measure thought disorder (Johnson & Holzman, 1979; Marengo, 1986; Liddle et al., 2002; Barrera, McKenna & Berrios, 2008). Many however, need to be used in conjunction with specific tests and the time pressure associated with the current study makes the utilisation of such scales impractical. For example, The Bizarre Idiosyncratic Thinking Scale (Marengo, 1986) requires the use of the Gorham Proverbs Test and the Comprehension Subtest of the Wechsler Adult Intelligence Scale (WAIS). The Thought

Disorder Index (Johnson & Holzman, 1979) needs to be administered in conjunction with the WAIS or Rorschach tests. The Thought and Language Index (TLI) (Liddle et al., 2002), includes ratings in response to the Thematic Apperception Test or the Rorschach test. The Thought Language and communication scale (TLC) includes measures of both positive and negative thought disorder and is easy to rate and score. Unlike the aforementioned ratings scales, it can also be used to rate any section of speech. While there are other thought disorder rating scales available which can also be used to rate any section of speech (CLANG, Chen et al. 1966), the TLC is the most widely used scale for the measurement of thought disorder (Barrera, McKenna & Berrios, 2008). The TLC was rated at the same time the CADSS was administered.

In terms of semantic tasks, implicit tasks were always administered first followed by the explicit tasks. People were not informed that the semantic tasks were implicit and explicit versions of one another. This was to reduce the likelihood of interference on the implicit measures. Order of the two implicit tasks was randomised across participants as was the order of the explicit tasks.

2.4.6 Implicit Tasks

2.4.6.1 Why Masked Priming was not employed

The technique of masked priming could have been employed in the current thesis to investigate implicit semantic access. After some consideration, it was decided that masking the implicit priming task would be inappropriate because (1) there is only a small body of schizophrenia examining masked indirect priming (Del Cul A, 2006; Kiefer, Martens, Weisbrod, Hermle, & Spitzer, 2009; Quelen, Grainger, & Raymondet, 2005a; Wentura, Moritz, & Frings, 2008) and (2) there is only the one analogue study for comparison (Angwin et al., 2004). Instead, a short SOA was used as there is a

wealth of data for comparison purposes, including a review (S. L. Rossell & Stefanovic, 2007) and meta-analysis (Pomarol-Clotet, Oh, Laws, & McKenna, 2008). Some might still argue that a semantic priming task with a short SOA and a distractor task might not meet the most stringent criteria for an 'implicit task' as there is still the possibility that participants might notice that some pairs are related. The differences between the implicit and explicit tasks used in this thesis do however, provide a reasonable divide between implicit and explicit access. The implicit task is defined by a short processing time and a distractor task, and the explicit task is associated with a longer processing time and directive instruction. This satisfies most definitions of the differences between implicit and explicit memory access. In terms of support from the literature, the terms 'implicit' and 'explicit' have been used to describe very similar tasks. There is support from the healthy (Rissman et al., 2003), schizophrenia (Kreher et al., 2009) and Alzheimer's literature (Rogers & Friedman, 2008) for our description of the implicit priming task. For the explicit task, support from Kraut who describes a directly related version of his Object task as explicit (Kraut, Moo, Segal, & Hart, 2002).

2.4.6.2 Semantic Priming

The stimuli for both priming tasks included 60 related word-word pairs and 30 word-pseudo-word pairs. From these stimuli, two word lists were created (A and B). In version A, 30 of the 60 word–word pairs remained related, while the other 30 pairs were re-arranged so that they now formed unrelated pairs. In version B, these relationships were counterbalanced, so that related pairs from list A were randomly re-assigned to create unrelated pairs, and the unrelated pairs were arranged back into their related word pairing. Thus, both lists A and B included 30 related word pairs, 30 unrelated word pairs and 30 pseudo-word pairs. The pseudo-word ratio was calculated at 50% (pseudo-word / pseudo-

word + unrelated pairs) (Neely, 1989) and the relatedness proportion was either 33% (based on calculations including all pairs) or 50% (if only real word pairs are considered). The stimulus onset asynchrony (SOA) was 950msec, the prime presentation was 200msec, the inter stimulus interval (ISI) was 750msec, the target was presented for 200msec and with an additional 2000ms response window. Participants were able to respond from the time the target appeared on screen. During ISI and the response window a central fixation cross was presented. Given that there were two testing sessions, the two lists were counterbalanced. The lists were matched on number of letters, syllables and phonemes in each word. Number of letters (3-10 letters), frequency, concreteness and imagability were also matched across lists. Pseudo-words were pronounceable and legally spelled letter strings (e.g. pont) and were selected from the ARC pseudo-word database (Rastle, Harrington, & Coltheart, 2002). These tasks can be considered implicit because participants are not told that the pairs they are responding to may be related. Instead, they are given a distracter lexical decision task. They are told to press one button if the second word of the pair is a real word and another button if it is a pseudo-word.

2.4.6.2.1 Direct Priming Task

Directly related word pairs used in this study included those with a direct semantic (i.e. SCOTCH-WHISKEY) or associative (i.e. DART-BOARD) relationship. All pairs had an association value > 10 in the Edinburgh Word Association Thesaurus (EAT: http://www.eat.rl.acu.au); the mean association value for the stimuli was 32.36.

2.4.6.2.2 Indirect Priming Task

Indirectly related word pairs describe those words related via their mutual association with a third concept. For example, LION-STRIPES are indirectly related via their association with TIGER. The EAT was used to ensure that there was no direct association between these pairs (all pairs <10).

2.4.7 Explicit Tasks

These tasks are explicit because participants are directed to consider the semantic nature of the relationships between pairs. In both explicit tasks, participants saw 32 pairs of words. Both the prime and target at the same time (prime above target). The stimuli remained on screen for 2.7 seconds and participants were given a further 1.5 seconds after stimuli disappeared from the screen to respond. This gave participants a total of 4.2 seconds to respond to each pair.

2.4.7.1 Association Task (direct)

In the Association Task, participants were presented with pairs of words, one above the other, and were asked to determine whether the pairs were associated with one another (e.g. CAT and DOG are related because they are pets) or not (CAT-PENCIL).

2.4.7.2 Object Task (indirect)

In the Object Task, participants were presented with pairs of words, one above the other, and were asked to judge whether the two words were connected via an association with a third word (e.g. HONEY and STING were presented and are connected via their association with BEE) or not (HONEY-BANGLE).

For all four tasks participants used a two button press, and were asked to respond as quickly and accurately as possible. Both accuracy and RT data were used for analysis.

2.4.8 Data Analysis

2.4.8.1 Data Analysis: Reaction Time

For each experimental group, all RT's more than two standard deviations from the mean for that group were replaced with the value two SD's from the mean this removed anticipatory responses <~100msec and delayed responses >~2000msec (Collins, 1999; Collins, 2002). This was for <5% of the data. Priming was calculated simply as 'unrelated – related'. There was no need to use the 'percentage gain' formulation often used with schizophrenia data (Nestor et al., 2006) given that the ketamine group were not significantly slower than placebo for any task (as below).

2.4.8.2 Data Analysis: Accuracy

The frequencies with which pseudo-words were classified as words (false positives) and words were classified as pseudo-words (false negatives) were recorded. Participants with more than 30% errors were excluded (Cohen, 1988). No participants were excluded on this basis.

Although the implicit and explicit tasks were designed to be as similar as possible a full factorial model 2 condition (ketamine, placebo) x 2 relatedness (related, unrelated) x 2 semantic prime types (direct, indirect) x 2 memory levels (implicit, explicit) was not possible due to procedural differences across the tasks in terms of stimuli presentation times, SOA and response windows. However, it was possible to perform a 2 condition x 2 relatedness x 2 semantic prime types repeated

measures analysis of variance at each memory level for RT and accuracy data. Post-hoc ANOVAs and t-tests were used to address specific hypotheses including examining whether there was significant positive indirect priming in the ketamine group but not the placebo. Post-hoc tests were Bonferroni corrected.

Exploratory correlations were used to examine the relationship between the semantic processing tasks and the symptoms data (TD and delusions specifically).

Lastly, paired samples t-tests were used to determine whether degree of psychotic symptomatology (measured using the TLC, SSS, and CADSS) differed between the ketamine and placebo conditions.

2.5 Results

2.5.1 Reaction Time Data

2.5.1.1 Implicit Tasks

Data is reported in Table 1.2 The repeated measures ANOVA with RT data found a main effect for relatedness ($F(1, 37) = 39.1$, $p<0.001$), reflecting an overall positive priming effect (unrelated RT > related RT). There was no main effect of prime type or condition, there were no two way or three way interactions. As it was hypothesised that ketamine would lead to increased indirect priming in comparison to the placebo condition further post-hoc comparisons were performed. Paired samples t-tests using the indirectly related word pairs showed there was significant priming only in the ketamine condition ($t= 2.40$, $M=23.32 \pm 42.42$msec, $p=0.02$) and not during placebo ($t=2.46$, $M=20.36 \pm 62.04$msec, $p=0.16$). Although no specific hypotheses were made for the direct condition, pair samples

t-test were performed to illustrate the comparison with the indirect condition. They found significant priming effects for both the ketamine (t= 3.79, M= 44.20 ± 50.87msec, p=0.001) and placebo condition (t=2.46, M= 26.32 ± 47.82msec, p=0.02).

2.5.1.2 Explicit Tasks

The repeated measures ANOVA with RT data found a main effect for relatedness ($F(1, 37) = 76.9$, $p<0.001$), reflecting an overall positive priming effect. There was also a main effect of prime type ($F(1, 37) = 51.7$, $p<0.001$), revealing that RTs were quicker for the direct task (Association) at 1494.85 ± 51.55msec compared to the indirect (Object) task (M=1716.94± 60.21msec). There was no main effect of condition or two or three way interactions. As above priming was confirmed for each task under each condition using paired samples t-tests. Direct Association Task: ketamine (t= -4.29, M=280.64 ± 285.18msec, p=<0.001) and placebo= (t= -3.01, M=185.94 ± 272.15msec, p=0.01); indirect Object Task: ketamine = (t= -3, M=197.88 ± 271.23msec, p= 0.008) placebo condition = (t=-7.03, M=251.55 ± 155.89msec p<0.001).

2.5.2 Accuracy Data

2.5.2.1 Implicit Tasks

The repeated measures ANOVA with error data found no main effects for relatedness, prime type or condition and there were no two way interactions. There was a three way interaction between relatedness, prime type and condition ($F(1, 37) = 4.5$, $p=0.05$). Paired samples t-tests were conducted to explore the interactions within each condition. In the direct task, participants under ketamine made significantly more errors in the unrelated (t= -2.82, p=0.01: M=96.32 ± 4.29) versus the related condition (M=98.60 ± 2.02, thus 2.3% priming). Under placebo, there were no significant differences

in accuracy for unrelated (t=0.83 p= 0.42, M=98.17± 2.29) versus related pairs (M=97.67± 0.42, thus 0.5% difference). Under ketamine, in the indirect task, there were no significant differences in error rates for unrelated (t=0.000 p=1.00, M=96.49 ± 2.83) versus related pairs (M=96.49 ± 2.19, thus 0.01% difference). Under placebo, there was also no difference in accuracy for related (t=-0.40 p=0.69: M=97.50 ± 2.13) versus unrelated pairs (M= 97.83 ± 2.71, thus 0.3% difference). Follow up one way ANOVA were conducted to explore interactions between conditions examining the degree of priming (defined as more errors in reaction to unrelated than related pairs) for each prime type. The results illustrated that there was greater priming in the direct prime type under ketamine (M=2.28 ± 3.52) than placebo (M=0.50 ± 2.71) (F (1, 38) = 7.68, p=0.01), but no difference in accuracy for indirectly related word pairs across ketamine (M=0.00 ± 4.71) and placebo (M=0.33 ± 3.73) (F (1,38) 0.06, p=0.81). Overall, there was significant priming for the direct task under ketamine (paired samples t-tests) and that this degree of priming was larger than that found under placebo (ANOVA). These effects were still significant when Bonferroni corrected for the 6 tests that were used to explain this three-way interaction (p=0.05/6). Although see caution noted in the discussion when interpreting these error results.

2.5.2.2 Explicit Tasks

The repeated measures ANOVA with error data found a main effect for group (F (1, 34) = 13.03, p=0.001) with the ketamine group (89.34% accuracy) being less accurate than the placebo (94.66% accuracy). There was a main effect for task (F (1, 34) = 24.34, p<0.001) with more errors in the indirect (89.44% accuracy) than direct (94.56% accuracy) task overall. There was no significant effect for relatedness (F (1, 34) = 3.33, p=0.08). There was a two way interaction between task and condition (F (1, 34) = 8.24, p=0.01). One way follow up ANOVAs examining task independently by

condition established that there was no difference in accuracy data between ketamine (93.09% accuracy) and placebo (95.78% accuracy) for the direct task ($F(1, 37) = 2.85$, $p=0.10$), but there was a difference for the indirect task ($F(1, 37) = 18.13$, $p=0.001$) with more errors made when on ketamine (85.29% accuracy) than placebo (93.59% accuracy). There was a relatedness and task interaction ($F(1, 34) = 21.83$, $p<0.001$) but no three way interaction.

Table 2.3 *Data from the Semantic Tasks*

Implicit/ Explicit	Task	Condition	Relatedness	Mean (SD) Reaction Time	Mean (SD) Accuracy
Implicit	Direct Priming	Ketamine	Unrelated	840.80 (154.24)***	96.32 (4.29)**
			Related	796.60 (123.76)	98.60 (2.02)
		Placebo	Unrelated	783.80 (160.64)*	98.17 (2.29)
			Related	757.48 (166.35)	97.67 (2.19)
	Indirect Priming	Ketamine	Unrelated	837.73 (143.87)*	96.49 (2.83)
			Related	814.42 (136.08)	98.60 (2.83)
		Placebo	Unrelated	788.48 (139.07)	97.50 (2.13)
			Related	768.12 (140.12)	97.83 (2.71)
Explicit	Object Task	Ketamine	Unrelated	1919.41 (354.42)**	91.54 (10.81)*
			Related	1721.53 (222.17)	79.04 (14.14)
		Placebo	Unrelated	1811.04 (408.76)***	96.38 (3.79)*
			Related	1559.50 (309.59)	90.79 (7.33)
	Association Task	Ketamine	Unrelated	1738.20 (469.00)***	90.79 (12.03)
			Related	1457.56 (325.81)	95.39 (5.04)
		Placebo	Unrelated	1471.78 (403.72)**	95.00 (5.21)
			Related	1285.84 (402.26)	96.56 (5.16)

Paired t tests (related vs unrelated) *p<.05 **p<.01 ***p<.001

2.5.2.3 Symptom Data

Symptom data was compared between the ketamine and placebo conditions by examining the ratings on the CADSS (the dissociation scale) the TLC (the thought disorder rating scale) and the SSS (the psychotic symptom rating scale). Prior to study participation, all participants completed the Schizotypal Personality Questionnaire (SPQ). No participant recorded a rating approaching the cut off of scores > 48.9 (M=8.95, SD=8.87). Comparisons using paired samples t-test found that participants endorsed significantly more symptoms on each scale following ketamine administration than they did following placebo (see Table 2.2).

Table 2.4 *Difference in Symptom Ratings Between Ketamine and Placebo*

Symptom Measure	Ketamine	Placebo	F	P
Clinician Administered Dissociative States Scale (CADSS) *(Scale range 0-92)*	11.71 (5.77)	1.15 (1.98)	13.46	<0.001
Thought, Language and Communication Scale (TLC) *(Scale range 0-63)*	4.23 (6.47)	0.10 (0.45)	28.54	0.01
Schizotypal Symptomology Scale (SSS) *(Scale range 0-144)*	36.11 (11.68)	11.79 (6.24)	6.29	<0.001
Schizotypal Symptomology Scale (SSS) – Delusion Subscale *(Scale range 0-30)*	2.00 (2.13)	0.68 (0.82)	10.47	0.02

The data in the current study demonstrated that, under the influence of ketamine, participants demonstrated an increase in indirect priming and an increase in errors on the Object Task. These variables were then correlated with the measures of delusions and thought disorder. Delusion severity was assessed via the SSS scale. The TLC scale measured thought disorder. To determine whether a relationship between semantic abnormalities and these symptoms existed, Pearson correlations were

performed. There was no significant relationship between the delusional subscale and errors on the Object Task (r= -0.27, n=16, p=0.32) or the degree of indirect priming (r=0.11, n=17, p=0.68). There was no significant relationship between TD and errors on the Object Task (r=-0.06, n=17, p=0.83) or indirect priming (r=0.20, n=19, p=0.42).

2.6 Discussion

This is the first study to compare implicit and explicit access to semantic memory after the administration of ketamine or a placebo with direct and indirect stimuli. The main findings were that on the indirect implicit task under the influence of ketamine participants showed greater RT priming than following placebo, which replicates findings in schizophrenia. For the explicit indirect task, following ketamine participants tended to make more errors but there were no RT differences for condition. For the direct implicit priming task, whist there were no differences in RT data, during the ketamine infusion participants were more likely to categorise unrelated words as pseudo-words than related, whilst there were no differences in the placebo group. The explicit direct task had no RT or accuracy condition differences. This data suggests implicit semantic access is more affected by ketamine than explicit. This confirms and extends previous analogue schizophrenia research using schizotypy populations (Morgan, Bedford, et al., 2006; Morgan et al., 2009)

2.6.1 Indirect priming

In the placebo condition, the RT data demonstrated that no significant implicit indirect priming had occurred. This is not uncommon finding among healthy controls (Chui, Gruber, Simpson, & Yurgelun-Todd, 2003; Moritz et al., 2002; Sass, Krach, Sachs, & Kircher, 2009), as indirect priming is more difficult to elicit than direct priming. Ketamine did not affect accuracy on this task. What is

interesting is that when participants were given ketamine, they produced a statistically significant indirect priming effect. Admittedly, some caution is required when interpreting this result given the lack of interaction during the repeated-measures analysis. However, this data does support the hypothesis that indirect priming would be significant under ketamine, a hypothesis based on the findings of a review and meta-analysis of the priming literature in schizophrenia (Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007). When interpreting such priming data, there are a number of theories available. The access/storage theory stipulates that semantic memory is either abnormally organised or accessed (or both) in schizophrenia which leads to unusual associations being made (Doughty et al., 2008; Forde & Humphreys, 1997; Rossell & David, 2006). Given that a single dose of ketamine is unlikely to disrupt the organisation of semantic memory, it is more likely that an access disorder explains these results. Access problems are thought to reflect an abnormally broad spread of activation in semantic memory (due to increased facilitation or decreased inhibition) (Collins & Loftus, 1975; McNamara, 2005; Moritz, Andresen, Naber, et al., 1999). In a healthy network, it is assumed that activation is limited to the concept being processed and its close relatives. This way, it can be assumed that primed pairs are closely related (as in a healthy network). If the spread extends beyond the usual boundaries of consideration, then distant relations will also be primed (as in schizophrenia). Given that this significant priming effect was produced specifically in the indirectly related word pairs condition it provides support for the utility of ketamine as a model for the semantic deficits associated with schizophrenia.

In terms of the Object Task (explicit/indirect), it was hypothesised more generally that there would be some abnormalities in performance under ketamine. RT performance was not impaired under ketamine however error data demonstrated that participants were less accurate in this condition. When

participants were asked to actively recognise indirect relationships, performance was reduced under ketamine suggesting a failure of conscious, strategic processing. These results suggest that, under the influence of ketamine, indirect relationships are processed abnormally.

2.6.2 Direct priming

Due to the degree of variation in results found in the literature, no specific hypotheses were made with regard to the direct implicit semantic priming task. Results showed that RT performance under ketamine was not significantly different from placebo performance. However, in terms of errors, the ketamine group tended to incorrectly classify more unrelated than related pairs as pseudo-words. A pattern of incorrectly classifying unrelated pairs as pseudo-words can reflect the utilisation of semantic matching processes (Neely, 1991). Semantic matching occurs when, after seeing both words of a pair, a participant decides that if the pair of words are related, then the target must be a word and if the pair are not related then the target is likely a pseudo-word. Reliance on this strategy can lead to the incorrect categorisation of targets in unrelated pairs as pseudo-words. This strategy is not reliant on the time interval between prime and target (referred to as stimulus onset asynchrony; SOA); it comes into play when the ratio of word to pseudo-word pairs is not 50/50 (Neely, 1989; Ober, Vinogradov, & Shenaut, 1995). In the current study, the proportions were 50/50 however, there is some data to suggest that individuals with schizophrenia demonstrate abnormal utilisation of this strategy (Ober et al., 1995; Vinogradov, Ober, & Shenaut, 1992). The authors are cautious however, with regard to over interpreting this finding; despite its statistical significance, the error data was very low overall for this task, suggesting that the participants were performing at ceiling. Further examination of error data with a more difficult version of this task, for example reducing presentation time of the stimuli, would be

needed to confirm the pattern reported here. For the explicit direct priming task, no effect of ketamine was observed; this is likely due to the relative ease of this task.

There have been two previous investigations of semantic priming after the administration of ketamine (Morgan, Rossell, et al., 2006; Stefanovic et al., 2009). Stefanovic did not report an effect of ketamine on indirect priming, but it is not possible to directly compare Stefanovic with the current experiment because of significant methodological differences including a lexical decision to both prime and target. In comparison, Morgan et al (2005) used a direct priming task only. In contrast to our work half their stimuli were high frequency and half of low frequency English words, ours were not divided in such a manner and were approximately of medium frequency. The major group difference in the Morgan study was that the ketamine group showed less priming with the low frequency words.

There were no differences in RT or accuracy data between conditions on the direct explicit Association Task. This finding supports the hypothesis that performance would be better on this direct explicit task in comparison to the indirect explicit task. Given the simple and highly structured nature of the task, this was not a surprising finding.

2.6.3 Symptom Data

It was hypothesised that semantic tasks affected by ketamine would correlate positively with the symptoms of TD and delusions as suggested in the schizophrenia literature (McKenna, 1991; Pomarol-Clotet et al., 2008; Rossell et al., 1999; Rossell & Stefanovic, 2007). The results did not support this hypothesis as neither TD nor delusional thinking correlated with either of the significant findings. While participants had significantly higher levels of thought disorder and delusions in the ketamine

condition, a closer examination shows that the actual levels of each symptom were still very low in this condition. This may explain why symptoms were not related to semantic processing in the current study. Other studies have reported negligible levels of TD (Pomarol-Clotet et al., 2006) but with dosing recorded differently (200ng/ml) direct comparisons are difficult. Adler (1998) and (1999) used the same TD rating scale and the same loading dose but a lower maintenance dose of ketamine (0.65mg/kg) but recorded higher levels of TD. More speech collection tasks were employed in their study and this may have contributed to the higher levels recorded. Direct comparisons are even more difficult in terms of delusions as no other study has used a subscale of the Schizotypal Symptomology Scale to collect delusion data. In the current study however, there was definite evidence of delusional thinking with one participant claiming the computer was deliberately trying to trick her, another was paranoid that he had wet himself, and another felt that he was being harshly judged by the researchers involved in the study; all thoughts that participants recognised as unusual after ketamine cessation. Further research using validated symptom measures such as the OLIFE would be useful (Mason & Claridge, 2006).

2.6.4 Limitations

Effect sizes in this study were smaller than those previously reported using ketamine administration (Morgan, Rossell, et al., 2006; Stefanovic et al., 2009). One potential reason for this is that this study used more semantic tasks in the session than other studies have. Increased awareness of semantic pairs can change the strategies that people use across the session. Given that the tasks were counterbalanced then this would have affected all the tasks equally, but also resulted in less clear priming across all the measures. Additionally, we used a continuous infusion so plasma levels were likely changing throughout the study, in addition rapidly developing tolerance to ketamine, or

tachyphylaxis, can develop across a single infusion. However again counterbalancing the tasks throughout the session should have in some way circumvented this. Practice effects are unlikely to explain the current results as half the participants completed their ketamine condition first and the other half placebo; this is the best design to circumvent this issue.

2.7 Conclusions

Ketamine administration did produce a very specific pattern of deficits that has been reported in schizophrenia; abnormalities in indirect semantic processing. In addition, there was some evidence of abnormal semantic matching – also seen in schizophrenia. The symptom data gathered did not support the relationship between semantic deficits and the symptoms of TD and delusions. Future research is needed to directly compare a schizophrenia sample using the same tasks so that more definite conclusions can be made.

CHAPTER 3. SCHIZOTYPY: IMPLICIT AND EXPLICIT SEMANTIC MEMORY

DECLARATION FOR THESIS CHAPTER 3

Declaration by candidate:

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, supervision of data collection, data analysis and writing of manuscript.	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Susan Rossell	Supervisor of Erica Neill's PhD. Responsible for study design. Provided assistance in data analysis and proof reading of the manuscript
Mariah Kordzadze	Recruitment and data collection

Candidates Signature:  **Date: 14/01/13**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from 2009

Susan Rossell Signature:  **Date: 14/01/13**

Declaration by candidate:

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, supervision of data collection, data analysis and writing of manuscript.	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Susan Rossell	Supervisor of Erica Neill's PhD. Responsible for study design. Provided assistance in data analysis and proof reading of the manuscript
Mariah Kordzadze	Recruitment and data collection

Candidates Signature: [redacted] **Date: 14/01/13**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from 2009

Mariah Kordzadze Signature: SIGNATURE NOT AVAILABLE

3.1 Chapter Guide

This chapter consists of an article that is under review with Neuropsychiatry Research. This is the second of four chapters concerned with implicit and explicit semantic function. Similar to Chapter Two, this chapter examines an analogue model of schizophrenia function: the schizotypy model.

3.2 Abstract

Schizotypy is a useful schizophrenia analogue that controls for confounding factors such as medication and general intellectual decline. In the current study this analogue approach was used to examine implicit/explicit and direct/indirect semantic memory function. This is the first study to examine both implicit and explicit semantic access in the same schizotypy sample. Participants completed four semantic tasks: (1) implicit indirect priming, (2) implicit direct priming, (3) explicit Object (indirect) task, and (4) explicit Association (direct) task. The schizophrenia literature suggests that semantic impairments are associated with thought disorder. As such, participants were divided into low (n=18) and high (n=18) schizotypy groups based on their responses to a thought disorder sub-scale of the Oxford Liverpool Inventory of Feelings and Experiences (O-Life) scale. In terms of implicit performance, the high schizotypy group demonstrated increased direct priming but non-significant indirect priming. The low schizotypy group demonstrated no difference in direct and indirect priming. Performance on the explicit tasks was equivalent between the two groups for direct stimuli. On the indirect explicit task, high schizotypy was associated with an increase in errors. Increased direct priming in high schizotypy is equivalent to that seen in schizophrenia, which has been interpreted as increased spreading of activation. Abnormal performance using the indirect stimuli was found across implicit and explicit versions. The relevance of these findings to schizophrenia are discussed..

3.3 Introduction

3.3.1 Semantic memory, schizophrenia confounds and schizotypy solutions

Semantic memory is described as our general knowledge store or our memory for meaning. This system allows us to recall factual rather than episodic memory (Kintsch, 1980; Tulving, 1972). Schizophrenia is associated with significant deficits in semantic memory (McKay et al., 1996). These deficits have been linked to symptoms such as thought disorder (Pomarol-Clotet et al., 2008), delusions (Rossell et al., 1999) and alogia (Rossell, 1999). One of the confounding factors complicating semantic memory research in schizophrenia is the effect of antipsychotic medication on memory (Green et al., 2002; Sumiyoshi, Sumiyoshi, Roy, Jayathilake, & Meltzer, 2006). A logical solution is to examine unmedicated participants however, this practice is ethically questionable (Bola, 2006). Alternatively, psychosis prone individuals can be examined. Psychosis proneness, often termed 'schizotypy', describes those individuals who have no diagnosable psychotic illness or obvious functional deficits but demonstrate tendencies towards psychotic symptomatology (Claridge, 1994, 1997). Analogue studies in schizotypy are thought to more accurately reveal the mechanisms involved in thinking in schizophrenia by eliminating confounding factors, including medication effects (Claridge, 1997; McCabe et al., 2005; Morgan et al., 2009).

3.3.2 Semantic memory, semantic priming, and deficits in schizophrenia

Semantic memory function in schizophrenia is often measured using semantic priming tasks. Performance on these tasks is generally interpreted in light of the spreading activation model of semantic memory structure. This model suggests that semantic memory is organised in a network with proximity between concepts determined by degree of relatedness (Collins & Loftus, 1975). Spread of activation occurs when a concept is stimulated which in turn transiently activates other concepts in

close proximity. In priming experiments, the semantic distance between concepts and the spread of activation in the network determine reaction time (RT) to word pairs. When a healthy individual completes a semantic priming experiment, concepts closely related to the prime are activated more quickly than concepts distantly related to the prime. Furthermore, while activation does spread to the further concepts, this spread takes longer and activation decays more rapidly.

Schizophrenia is associated with semantic priming deficits (Chui et al., 2003; Rossell & David, 2000; Vinogradov et al., 1992; Weisbrod et al., 1998). Of the varying priming paradigms, the one to provide the most consistent and compelling results are indirect priming tasks. While directly related pairs include stimuli like TEA-COFFEE, indirectly related stimuli include those more distantly related, usually via a third concept so, for example TEA-BEAN (connected by COFFEE). While healthy respondents are typically quicker to respond to direct than indirect pairs (Sass et al., 2009), schizophrenia results are characterised by enhanced indirect priming (Rossell & Stefanovic, 2007). The spreading activation model is able to account for this effect suggesting that it reflects a failure of inhibition in the network. As a result of this failure, distant associations, which would normally be inhibited, remain available in schizophrenia leading to enhanced indirect priming. This unusual finding and its interpretation have been supported by a review (Rossell & Stefanovic, 2007) and a meta-analysis (Pomarol-Clotet et al., 2008). Both of which suggest that this effect is exacerbated among those with thought disorder. The link between thought disorder and semantic disturbance has support from both the priming literature and other semantic measures including fluency tasks (Goldberg et al., 1998; Stirling, Hellewell, Blakey, & Deakin, 2006).

Schizotypy has been used to model these semantic priming deficits. Tasks using directly related stimuli have provided mixed results. Some report increased priming (Moritz, Andresen, Naber, et al., 1999; Niznikiewicz et al., 2002) while others report the opposite pattern (Morgan, Bedford, et al., 2006). In terms of indirect tasks, a majority of papers confirm the increased indirect priming effect in high schizotypy (Johnston et al., 2008; Moritz, Andresen, Naber, et al., 1999; 2008; Pizzagalli et al., 2001). In terms of thought disorder, two of the indirect studies found a relationship between language (thought disorder measures) and enhanced indirect priming (Johnston et al., 2008; Moritz, Andresen, Domin, et al., 1999). Reduced indirect priming has also been reported (Kiang, Prugh, & Kutas, 2010) with no relationship between language disturbance and indirect priming found when electrophysiological measures (the N400) were examined.

3.3.3 Implicit and explicit semantic processing

While traditional semantic priming tasks have been explored in both schizophrenia and schizotypy with some intriguing findings, an area of semantic function that has been neglected is the influence of implicit and explicit processing on priming performance. Implicit retrieval occurs outside of conscious awareness whilst explicit retrieval requires conscious effort (Horan et al., 2008). There is evidence of dissociations in implicit and explicit performance in amnestic patients (Gabrieli et al., 1995) and the elderly (Gopie et al., 2011). Some studies have found differences across episodic and semantic memory in terms of implicit and explicit access (Danion et al., 1989). The study by Danion found that implicit and explicit access were differently affected by diazepam (an anxioltyic), suggesting that access is not necessarily the same for the two memory systems. Studies of implicit and explicit semantic access in Alzheimer's have found poor explicit semantic and reduced but less impaired implicit access (Rogers & Friedman, 2008). Despite the knowledge that semantic memory is impaired

in schizophrenia, and that implicit and explicit semantic access can be differentially impaired in other conditions, very little research has been done to investigate these different access routes separately for semantic memory in schizophrenia and schizotypy.

Semantic priming tasks, designed to tap into automatic processing, may be regarded as implicit due to the fact that they (1) provide a distractor task to avoid awareness of the tasks focus and (2) do no allude to the true nature of the task (Kreher et al., 2009; Kuperberg et al., 2008; Neill et al., 2011; Rissman et al., 2003; Rogers & Friedman, 2008).

Explicit semantic tasks include instructions directing attention to the semantic relatedness of stimuli. Participants are told to use semantic categories in the formulation of responses or to judge semantic category membership (Giffard et al., 2001). Moelter (2005) used the Pyramids and Palm Trees Battery (an explicit semantic battery) and found no difference between the schizophrenia and control sample. When explicit tasks use indirect stimuli however, deficits in explicit semantic processing have been reported (Assaf et al., 2007). Assaf used the Object Task created by Kraut (Kraut, Moo, et al., 2002) in which participants were required to determine whether two words, for example HONEY-STINGS, evoked the idea of another concept (BEE). The results showed that on this task, schizophrenia participants demonstrated slower response times to unrelated pairs and incorrectly categorised unrelated pairs as related significantly more often (unrelated pair example: HONEY-NUMBER). (Johnston et al., 2008; Kiang et al., 2010; Morgan, Bedford, et al., 2006; Morgan, Rothwell, Atkinson, Mason, & Curran, 2010; Moritz, Andresen, Naber, et al., 1999; 2008; Niznikiewicz et al., 2002; Pizzagalli et al., 2001).

There is very little data on explicit semantic processing in schizotypy. One study examined ERP's (Kimble et al., 2000) using a task similar to the silly sentences task originally created by Collins and Quillian (1969) and found that like schizophrenia, high schizotypy was associated with a reduced N400 effect (a measure of semantic processing). One paper (Mohr, Graves, Gianotti, Pizzagalli, & Brugger, 2001) found that high schizotypy was associated with a pattern of incorrectly classifying unrelated pairs as related matching the findings from the schizophrenia data (Assaf et al., 2007).

The current investigation will extend previous research by examining responses to direct and indirect stimuli on both implicit and explicit tasks in one sample. In addition, the explicit tasks have been chosen on the basis that they have previously been used in schizophrenia studies.

3.3.4 Aims and hypotheses

The aim of this study was to examine semantic memory function in relation to high and low thought disorder schizotypy groups. In the current study we used the Oxford Liverpool Inventory of Feelings and Experiences (O-LIFE) (Mason & Claridge, 2006) to score schizotypy on the cognitive disorganisation scale (the thought disorder scale). High and low groups were defined as the bottom and top thirds of the sample. Participants completed a test battery that examined implicit and explicit access to semantic memory using both directly and indirectly related word pairs. It was proposed that (1) all participants will be quicker and more accurate in responding to direct pairs than indirect pairs (Assaf et al., 2007; Sass et al., 2009) within implicit and explicit conditions. For task one, *implicit indirect priming*, it was hypothesised that (2) the high schizotypy group would demonstrate increased indirect priming (Rossell & Stefanovic, 2007). For task two, *implicit direct priming*, given the heterogeneity of direct priming results found in schizophrenia and schizotypy, no specific hypothesis were made. For

task three, *explicit indirect*, a task using the same format as the Object Task created by Kraut (2002) was used to examine explicit access to indirect associations. Schizophrenia samples and those with high magical beliefs categorise unrelated pairs as related more often and are slower on this task (Assaf et al., 2007; Mohr et al., 2001). Thus, it was hypothesised that (3) high schizotypy will be associated with abnormalities (RT and errors) on the Object Task. For task four, *explicit direct*, a basic Association Task was used as a measure of explicit, direct access to semantic memory and requires participants to determine whether pairs are related (CAT-DOG) or not (CAT-PENCIL). This exact task has not been used in schizophrenia but it is necessary to have an explicit version of the direct priming task to have a balanced design. We predicted that (4) in comparison to the explicit indirect task (Object Task) there will be no group differences on the explicit direct task (Association) given that specific instructions are provided to extract the semantic relationships and participants have ample time to assess the pairs of words on the screen at the same time for a reasonably extended period (2.7 seconds to process the pair). Therefore, even if the high schizotypy group had minor cognitive difficulties (which have been reported in the literature) (Spitznagel & Suhr, 2002) they would be compensated for by the tasks structure.

3.4 Methods

3.4.1 Participants

55 individuals (23 males and 32 females) between the ages of 18-32 years of age were recruited. The mean age of all participants was (M=23.6; SD=3.3). The inclusion criteria included no prior history of mental illness or anti-psychotic medication use. The participants were recruited via advertisements at Monash University. All participants completed the O-LIFE questionnaire (159 YES/NO statements relating to unusual beliefs or experiences). Four factors are obtained from the O-

LIFE: unusual experiences (UNEX), which refers to unusual perception and fantasy thoughts; introvertive anhedonia (INVAN), which measures difficulties in attaining pleasure from social situations, preference for solitude and is related to negative symptoms; impulsive non-conformity (IMPNON), which explores asocial behaviour; and finally, cognitive disorganisation (CogDis), which records aspects of poor attention and concentration. It is thought to reflect thought disorder and other disorganised aspects of psychosis, thus making it the most appropriate scale to utilise in the current study. The O-LIFE CogDis scores served to divide the top and bottom thirds of the sample for the second phase. The alternative method is to use a median split. The three way split was chosen because research suggests that performance of a median split followed by ANOVA's fails to make maximum use of the variance in the data (see Fernyhough, Jones, Whittle, & Waterhouse, 2008; Field, 2005). The low group included N=18 participants who scored 0-7 and the high group included the N=18 participants scoring 14-22 with possible scores ranging between 0-24. Age, education (missing data for 5 participants), gender and National Adult Reading Test (NART; Nelson, 1982; an estimate of a premorbid verbal IQ); was recorded for all participants. Participants were tested on the four semantic tasks.

3.4.2 Priming Tasks

For all priming tasks, stimuli were between 3-10 letters and the direct and indirect tasks were matched on frequency, concreteness and imagability. Pseudo-words were pronounceable and legally spelled letter strings (e.g. pont) and were selected from the ARC pseudo-word database (Rastle et al., 2002).

3.4.3 Implicit Semantic Tasks

One *direct* and one *indirect* version of a semantic priming task were administered. The stimuli for both priming tasks included 60 related word-word pairs and 30 word-pseudo-word pairs. From these stimuli, two word lists were created (A and B). In version A, 30 of the 60 word–word pairs remained related, while the other 30 pairs were re-arranged so that they now formed unrelated pairs. In version B, these relationships were counterbalanced, so that related pairs from list A were randomly re-assigned to create unrelated pairs, and the unrelated pairs were arranged back into their related word pairing. Thus, both lists A and B included 30 related word pairs, 30 unrelated word pairs and 30 pseudo-word pairs. The pseudo-word ratio was calculated at 50% (pseudo-word / pseudo-word + unrelated pairs) (Neely, 1989) and the relatedness proportion was either 33% (based on calculations including all pairs) (Rossell & Stefanovic, 2007) or 50% (if only real word pairs are considered) (Minzenberg et al., 2002). These were presented at a short Stimulus Onset Asynchrony (SOA: the time between the prime and the target) of 250msec (primes were presented for 200msec, and an inter stimulus interval (ISI) of 50 msec). The SOA was kept short to ensure that participants were processing the information implicitly. There are no definite rules dictating what is a short or long SOA; although, a review by Rossell and Stefanovic (2007) found that a majority of studies which successfully invoked automatic processing with SOAs<400ms. The target was presented for 200msec and with an additional 2000ms response window. Participants were able to respond from the time the target appeared on screen. During ISI and the response window a central fixation cross was presented(Rastle et al., 2002). The lists were matched on number of letters, syllables and phonemes in each word. The direct task used directly related prime-targets which were members of the same category (e.g. UNCLE - AUNT) and the indirect used indirectly related prime-targets (e.g. TEA - (coffee not presented) - BEAN) (although care was taken not to repeat words across the two versions).

The instructions were to read both words and identify whether the second word was real or made up (by pressing a 'yes' or 'no' button). Accuracy and reaction time were recorded for analysis.

3.4.4 Explicit Semantic Tasks

These tasks are explicit because participants are directed to consider the semantic nature of the relationships between pairs. In both explicit tasks, participants saw 32 pairs of words. Both the prime and target were presented at the same time (prime above target). The stimuli remained on screen for 2.7 seconds and participants were given a further 1.5 seconds to respond. The Association Task is an explicit version of a *direct* semantic priming task and requires participants to identify word associations. Participants were presented with 16 associated pairs and 16 unrelated pairs. The Object Task was an explicit version of the indirect priming task. Participants were presented with 16 pairs associated by a third word, i.e. HONEY and STING to BEE, and 16 that had no association to a third word. Both tasks used a 2-button press they responded to whether the pairs made them think of a third concept/formed a third concept. Participants were given practice trials to ensure that they understood how to do this task. Accuracy and reaction time were recorded for analysis.

Tasks were always given in the following order: (1) indirect semantic priming, (2) direct semantic priming (3) Object task (4) Association task. The implicit were done first to reduce the likelihood that participants would work out the presence of semantic relationships. The indirect priming task was given first to avoid the possibility that after direct priming, indirect pairs might be processed as unrelated. The order of the explicit tasks was not so important but was consistent between participants.

3.4.5 Data analysis

Demographic data were analysed with independent groups ANOVA and Chi-squared. RTs and accuracy data for both, the implicit and explicit tasks were subjected to a 2x2x2 repeated measures ANOVA with a between subjects factor of Groups (high or low schizotypy), and the 2 within subjects factors of Relatedness (related or unrelated pairs), and condition (direct or indirect). When significant interactions emerged involving the relatedness factor, the level of priming effect was computed (unrelated-related RT) and used in post-hoc analysis. Given the differences in task timing across the implicit and explicit measures it was deemed inappropriate to complete a 2x2x2x2 ANOVA.

3.5 Results

Table 3.1 shows means and standard deviations for demographic data. There was no significant difference between the high and low schizotypy groups in age ($F(1, 34) = 1.1$; $p = 0.3$), NART IQ ($F(1, 34) = 0.7$; $p = 0.4$), education ($F(1, 29) = 2.2$; $p = 0.1$), or gender ($X^2(1, n = 36) = 0.0$, $p = 1.0$). The high schizotypy group scored higher on all four scales of the O-LIFE: UNEX ($F(1, 34) = 14.4$, $p = 0.001$); CogDis ($F(1; 34) = 361.8$, $p = 0.001$); INTAN ($F(1; 34) = 10.9$, $p = 0.003$) and IMPNON ($F(1; 34) = 9.4$, $p = 0.004$).

Table 3.1 *Demographic and O-LIFE Data.*

Group		Low Schizotypy, N = 18	High Schizotypy, N = 18
Male / Female		8/10	8/10
Age (years)		22.72 (2.94)	23.94 (3.75)
Education (years)		16.5 (2.1)	15.4 (2.1)
NART IQ		109.83 (6.71)	107.89 (7.55)
OLIFE	UNEX	5.67 (5.40)	12.33 (5.17)***
	CogDis	4.28 (2.37)	18.06 (1.95)***
	INTAN	3.33 (3.67)	7.67 (4.16)**
	IMPNON	8.00 (3.16)	10.72 (2.05)**

*p<.05; ** p<.01; *** p<.001

3.5.1 Reaction Time Data

3.4.1.2 Implicit Tasks: The 2x2x2 ANOVA showed a main effect for relatedness ($F(1, 34) = 24.01$, $p<0.001$), reflecting an overall positive priming effect (unrelated RT (M= 659ms ± 102) > related RT (M= 633ms ± 103, d=0.25) and there was a main effect for condition: direct (M= 661ms ± 93) and indirect (M= 632ms ± 119), ($F(1, 34)= 6.7$, $p= 0.01$, d=0.27) with participants responding faster to indirect than direct pairs. There was a two way interaction between relatedness and condition ($F(1, 34) = 12$, $p= 0.01$) and a three-way interaction between group, relatedness and condition ($F(1, 34) = 10.6$, $p= 0.01$). As it was hypothesised that the high schizotypy group would demonstrate increased priming in the indirect condition, further post-hoc analysis was performed separately for the direct and indirect tasks. Independent samples t-tests were used to establish that there was more *direct*

priming (t (34) = -2.11p= 0.04, d=-0.7) in the high (52ms) than low (28ms) schizotypy group. There was a trend towards a significant difference between groups in the *indirect* condition (t(34)= 1.99, p= 0.05, d=0.65), but with more priming in the low (27ms) than the high (-3ms) schizotypy group (see Table 3.2 and figure 3.1 for priming results and Table 3.3 and Figure 3.2 for related and unrelated raw scores).

3.5.1.3 Explicit Tasks: The 2x2x2 ANOVA established that there was a main effect for condition (F (1, 34) = 40.7, p < 0.001, d= -1.35) with participants responding faster to direct (M= 1179ms ±190) than indirect pairs (M= 1468ms ± 236). There was also a main effect for relatedness (F (1, 34) = 26.2, p < 0.001, d= -0.69) with participants responding faster to related (M= 1260ms ±178) than unrelated pairs (M= 1387ms ± 186). There was no main effect of group nor were there any interactions (see Table 3.3 for related and unrelated raw scores).

Table 3.2 *Semantic Task Data: RT Priming*

Group		Low	High	Cohen's d	F(1,34)	p
Implicit	Direct	28 (39)	53 (31)	-0.70	4.5	0.04
	Indirect	27 (42)	-3 (50)	0.65	4.0	0.05
Explicit	Direct (Association)	162 (135)	132 (161)	0.20	0.4	0.6
	Indirect (Object)	87 (237)	126 (200)	-0.18	0.3	0.6

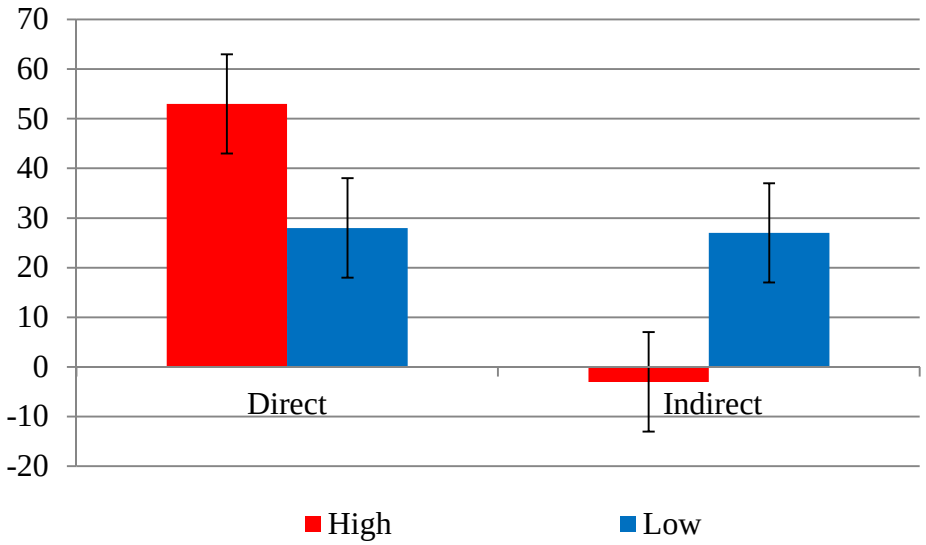

Figure 3.1 Implicit Semantic Priming

Table 3.3 *Semantic task data: RT*

Implicit/Explicit	Condition	Group	Relatedness	Mean (SD) Reaction Time in msec	Mean (SD) Accuracy
Implicit	Direct Priming	High	Unrelated	681 (71)	99.07 (1.54)
			Related	628 (72)	96.85 (2.67)
		Low	Unrelated	681 (112)	97.59 (2.51)
			Related	653 (116)	97.59 (3.76)
	Indirect Priming	High	Unrelated	611 (63)	95.56 (7.50)
			Related	614 (72)	96.66 (3.62)
		Low	Unrelated	665 (159)	97.40 (4.36)
			Related	638 (157)	96.85 (3.70)
Explicit	Association Task (Direct)	High	Unrelated	1248 (233)	96.53 (7.80)
			Related	1116 (248)	97.92 (4.79)
		Low	Unrelated	1257 (171)	95.83 (5.25)
			Related	1095 (159)	93.75 (6.78)
	Object Task (Indirect)	High	Unrelated	1551 (293)	94.79 (6.16)
			Related	1425 (261)	80.21 (12.36)
		Low	Unrelated	1493 (263)	95.83 (7.43)
			Related	1406 (229)	86.46 (10.77)

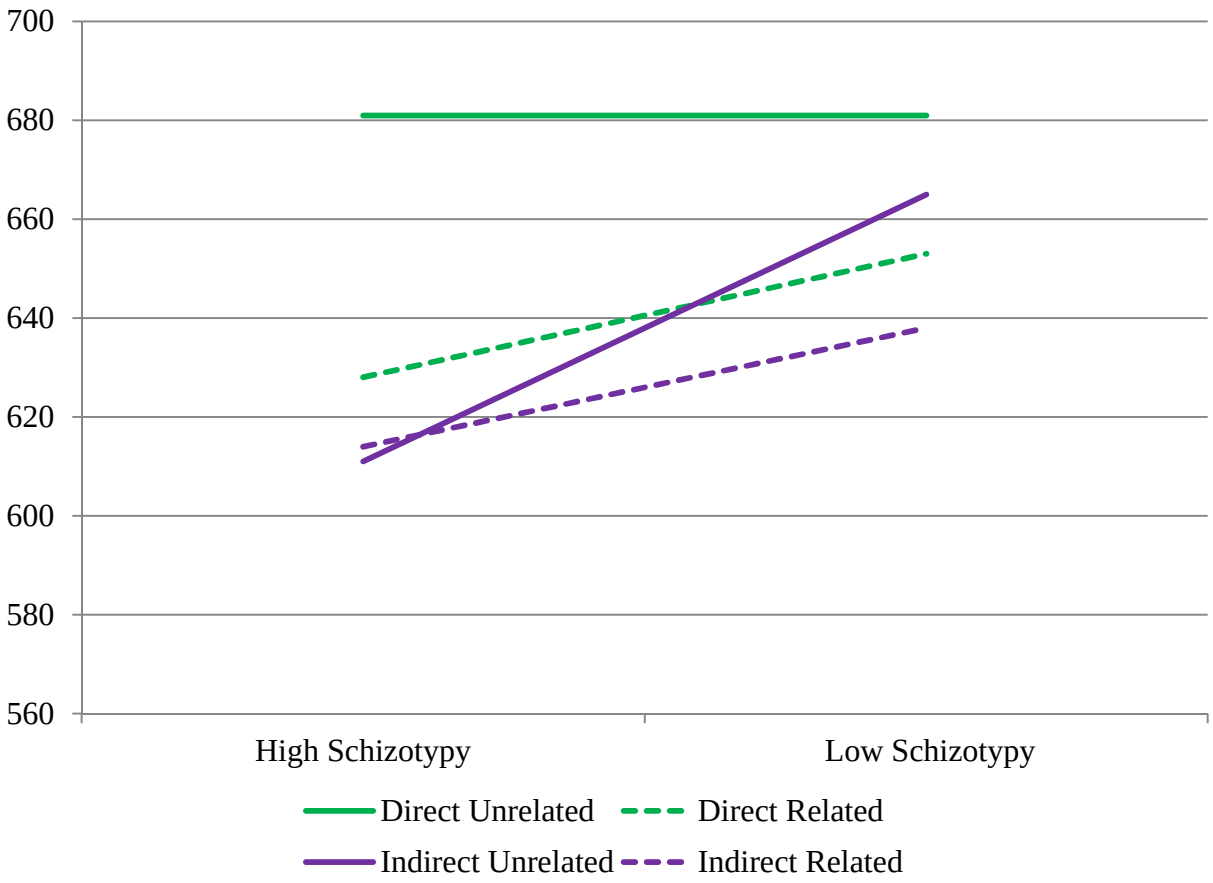

Figure 3.2 Raw Reaction Time Data for Implicit Priming Tasks

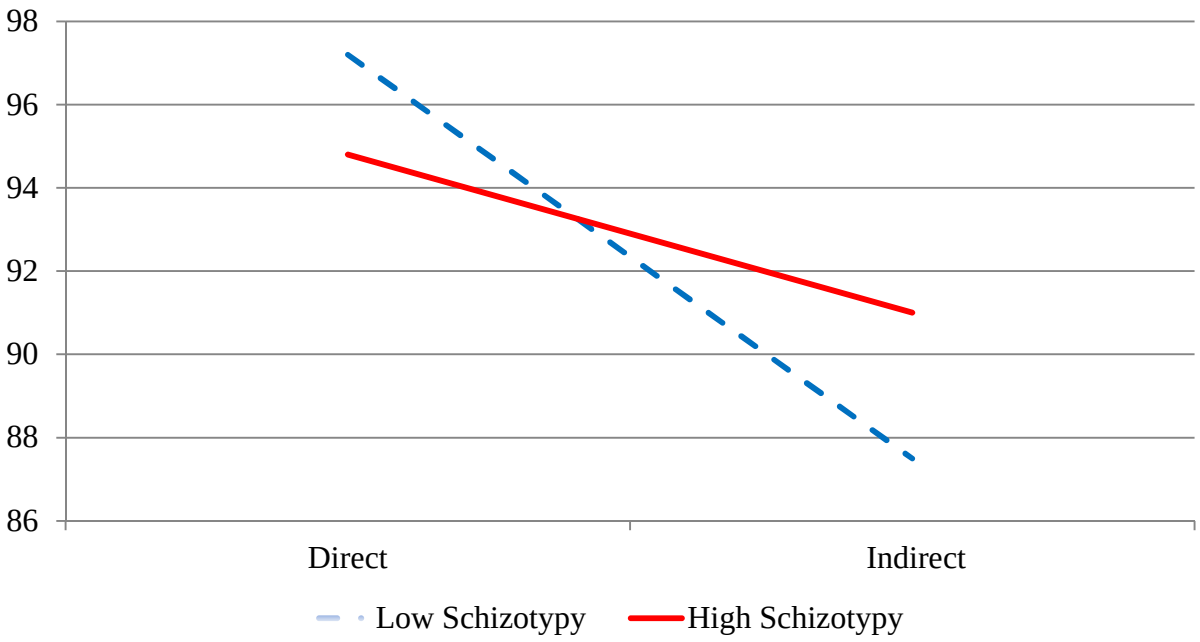

Figure 3.3 Percentage Correct Responses to Explicit Tasks

3.5.2 Error Data

3.4.2.1 Implicit Tasks: The 2x2x2 ANOVA showed no main effects or interactions for error data.

3.4.2.2 Explicit Tasks: The 2x2x2 ANOVA established main effects for relatedness ($F(1, 34) = 13.6$, $p < 0.001$, $d = -0.98$) and condition ($F(1, 34) = 77.5$, $p < 0.001$, $d = 1.37$), but no group main effect. Errors were greater for the related pairs ($M = 10\% \pm 7$) compared to the unrelated pairs ($M = 4\% \pm 5$); they were further higher for the indirect task ($M = 11\% \pm 6$) compared to the direct task ($M = 4\% \pm 4$). There were two way interactions between condition and group ($F(1, 34) = 16.0$, $p < 0.001$) and between condition and relatedness ($F(1, 34) = 18.9$, $p < 0.001$). To explore the interaction between condition and group, an independent samples t-test was conducted comparing the difference in percentage of

errors made on the association versus the object task separately for the low and high groups. Compared to the low group (M= 4% ± 4) the high group made significantly more errors on the indirect versus the direct task (M= 10% ± 5), t (34) = -4, p< 0.001, d=1.35) (See Figure 3.3).

3.6 Discussion

With regards to hypothesis (1): All participants will be quicker and more accurate on the direct association conditions than indirect, the data supported this for the explicit tasks with main effects for condition using both RT and error data. For the implicit tasks, RT data did not support this hypothesis. Instead, responses were characterised by faster average RT's to indirect rather than direct stimuli for both the high and low group. Practice effects do not explain this result as indirect priming was always completed first (Spitzer, Braun, Hermle, & Maier, 1993). An examination of the data suggests that this finding is due to the high group's failure to prime in the indirect condition; reflecting a failure to recognise the relationship between related pairs (See Figure 1).

Hypothesis (2): 'High schizotypy will be associated with greater priming in the implicit indirect task', was not supported by the results. Instead, high schizotypy was associated with increased direct but not indirect priming. While this finding was not hypothesised, there is literature to support enhanced direct priming in schizotypy (Moritz, Andresen, Naber, et al., 1999; Niznikiewicz et al., 2002). Previous research has suggested that akin to increased indirect priming, increased direct priming reflects greater spreading activation. It may be that in this sample, the spread is greater than average but not as extreme as that seen in schizophrenia. A number of research papers in schizotypy have, however, reported increases in both direct and indirect priming amongst high schizotypy groups (Moritz, Andresen, Domin, et al., 1999; Pizzagalli et al., 2001). The reason for the failure of indirect

priming in the current study may be attributable to lower levels of schizotypy in the current sample. It is difficult to compare to other studies, however, as Moritz (1999) used a language disturbance measure and Niznikiewicz (2002) included participants with a diagnosis of schizotypal personality. In addition, to different levels of schizotypy, it is also possible that analogue thought disorder symptoms were higher in previous studies. Moritz split his group based on the language questions contained in the Frankfurt Complaint Questionnaire and although the CogDis includes thought disorder questions, it is not exclusively language based. Niznikiewicz included schizotypal personality participants who likely had more severe psychotic symptomatology than a high schizotypy group.

3.6.1 Low schizotypy: Implicit priming

The finding of equivalent priming for direct and indirectly related pairs in the implicit condition for the low schizotypy group is also interesting and unexpected. This finding may stem from the way the participants were divided into high and low groups. A majority of schizotypy priming papers have used correlational analysis (Johnston et al., 2008) or have opted to do a median split to divide their participants (Mohr et al., 2001; Moritz, Andresen, Domin, et al., 1999). In the current study, the groups were divided using a three way split including only the top and bottom third of participants. The only other study to use a three-way split of the O-LIFE (Morgan, Bedford, et al., 2006) did not include indirect stimuli, so comparisons cannot be made. There is very little research focusing on the cognitive/personality profiles of individuals scoring extremely low on schizotypy, but it has been suggested that they do not represent the norm (Bowman & Thunbull, 2008; Nettle, 2006) . Both papers make links between autism and low schizotypy. Further, as yet unpublished data from Neill and Rossell examining priming performance in schizophrenia, using the same implicit priming tasks, found the same pattern in a chronic low thought disordered group.

3.6.2 Explicit results

Hypothesis (3): High schizotypy individuals will demonstrate abnormal performance on the explicit indirect task. This hypothesis was supported with regards to error data. and is in line with findings from the schizophrenia literature (Assaf et al., 2006). The interaction (See Figure 3) shows that the SZ group showed greater errors to indirect pairs; opposite to the pattern demonstrated by the low schizotypy group. Hypothesis (4) proposed that there would be no group differences in performance on the Association task and this was supported by the results. The Association task provided participants with specific instructions and gave ample time to assess the pairs of words on the screen at the same time for a reasonably extended period (2.7 seconds to process the pair). These factors would have compensated for any mild cognitive deficits that the high schizotypy group may have had.

3.7 Conclusion

The present study examined explicit and implicit semantic memory in high schizotypy. Abnormalities were found in both direct and indirect implicit processing. Further, these patterns supported schizophrenia findings. It was also interesting to note that low schizotypy was associated with abnormal performance. Future research should examine the high and the middle group of a three way split or perhaps compare all three groups to determine the effect of low and high schizotypy separately from those who fall somewhere between the extremes. Further, future studies would benefit from including the same stimuli in the implicit and explicit tasks.

CHAPTER 4. SCHIZOPHRENIA: IMPLICIT AND EXPLICIT SEMANTIC MEMORY

DECLARATION FOR THESIS CHAPTER 4

Declaration by candidate:

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, data collection, data analysis and writing of manuscript.	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Susan Rossell	Supervisor of Erica Neill's PhD. Provided assistance in data analysis and proof reading of the manuscript

Candidates Signature: [redacted] **Date: 14/01/13**

Declaration by co-authors

The undersigned hereby certify that:

(7) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(8) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(9) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(10) there are no other authors of the publication according to these criteria;
(11) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(12) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from 2009

Susan Rossell Signature: [redacted] **Date: 14/01/13**

4.1 Chapter Guide

This chapter consists of the article that is currently in press with Psychiatry Research (see Appendix D). There is no additional information included in this chapter beyond what was submitted to Psychiatry Research as the additional background information associated with this chapter was covered in Chapter One. Specifically, section 1.2.4 describes implicit and explicit memory in detail and under section 1.4 there is extensive detail of how semantic priming tasks are created.

4.2 Abstract

Semantic memory deficits in schizophrenia (SZ) are profound, yet there is no research comparing implicit and explicit semantic processing in the same participant sample. In the current study, both implicit and explicit priming are investigated using direct (LION-TIGER) and indirect (LION-STRIPES; where tiger is not displayed) stimuli comparing SZ to healthy controls. Based on a substantive review (Rossell & Stefanovic, 2007) and meta-analysis (Pomarol-Clotet et al., 2008) it was predicted that SZ would be associated with increased indirect priming implicitly. Further, it was predicted that SZ would be associated with abnormal indirect priming explicitly replicating the work of Assaf et al. (2006). No specific hypotheses were made for implicit direct priming due to the heterogeneity of the literature. It was hypothesised that explicit direct priming would be intact based on the structured nature of this task. The pattern of results suggest (1) intact reaction time (RT) and error performance implicitly in the face of abnormal direct priming and (2) impaired RT and error performance explicitly. This pattern confirms general findings regarding implicit/explicit memory impairments in SZ whilst highlighting the unique pattern of performance specific to semantic priming. Finally, priming performance is discussed in relation to thought disorder and length of illness.

4.3 Introduction

4.3.1 Semantic deficits in schizophrenia

Semantic memory is described as our "general knowledge store" (Kintsch, 1980; Tulving, 1972) and theory suggests that it is organised in such a way that related ideas are stored together in a network of concepts (Minzenberg et al., 2002). The idea that a disruption to one's understanding and memory for general knowledge contributes to schizophrenia symptomatology is appealing. Investigators have suggested a link between psychotic symptoms and impaired general knowledge for over a century (McKenna & Oh, 2005). Statements alluding to dysfunction in the semantic system have included the idea of a 'weakness of stored regularities' (Hemsley, 1987) or 'deficient real world knowledge' (Cutting & Murphy, 1988). The semantic deficits associated with SZ have been investigated using various tasks including fluency measures (Bokat & Goldberg, 2003; Henry & Crawford, 2005), 'silly sentences' tasks (Rossell et al., 1998) and, most commonly, semantic priming tasks (Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007). Priming tasks require participants to respond to word pairs and the priming effect describes the speeded response to those pairs that are related (CAT-DOG) over those that are unrelated (CAT-BANANA).

4.3.2 Direct v. Indirect Priming

Priming studies generally use pairs that are directly related through category (DRUM-PIANO) or association (DRUM-BEAT). The results in SZ using directly related pairs are mixed. Some research finds increased (Chenery et al., 2004; Rossell & David, 2006; Weisbrod et al., 1998), some decreased (Aloia et al., 1998; Besche et al., 1997; Ober, Vinogradov, & Shenaut, 1997; Passerieux et al., 1997; Rossell & David, 2000) and some normal (Chapin, McGowan, Vann, Kenney, & Youssef, 1992; Minzenberg, Poole, Vinogradov, Shenaut, & Ober, 2003; Quelen et al., 2005; Spitzer, Braun, Hermle,

& Maier, 1993; Surguladze, Rossell, Rabe-Hesketh, & David, 2002) priming. The reason for variations in results have been attributed to differences in task design and participant demographic and symptom profiles (Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007). Indirectly related pairs are also used in semantic priming research. Indirect pairs describe those related by a third concept so, for example TEA-BEAN (connected by COFFEE). While healthy participants are typically quicker to respond to direct than indirect pairs (Sass et al., 2009), a review of those studies using indirect stimuli in SZ suggests that results are characterised by enhanced indirect priming (Rossell & Stefanovic, 2007). The spreading activation model is able to account for this effect suggesting that it reflects a failure of inhibition in the network. As a result of this failure, distant associations which would normally be inhibited remain available leading to enhanced indirect priming. This unusual finding, and its interpretation, have been supported by a review (Rossell & Stefanovic, 2007) and a meta-analysis, especially amongst those with thought disorder (Pomarol-Clotet et al., 2008).

4.3.3 Implicit v. Explicit Access

There is evidence of dissociations in implicit and explicit memory function. This data comes from the performance of amnestic patients (Gabrieli et al., 1995) and the elderly (Gopie et al., 2011). In addition, some studies have found differences in implicit and explicit access across episodic and semantic memory (Danion et al., 1989). Studies of Alzheimer's patients find greater impairments during explicit than implicit semantic access (Rogers & Friedman, 2008). Despite the knowledge that semantic memory is impaired in SZ (McKay et al., 1996), and that implicit and explicit semantic access can be differentially impaired in other conditions, very little research has investigated these different access routes separately and comparatively for semantic memory in SZ.

Semantic priming experiments are generally regarded as implicit in nature due to the fact that they (1) do not allude to the true nature of the experiment, and (2) provide a distractor task to further reduce awareness of the experiments true purpose (Kreher et al., 2009; Kuperberg et al., 2008; Neill et al., 2011; Rissman et al., 2003; Rogers & Friedman, 2008). The distractor task often includes a pseudo word as the second word in the pair (CAT-VOSH), and the participants are instructed to determine whether the second word from each pair is real or not. Explicit semantic tasks on the other hand include instructions directing attention to the semantic relatedness of stimuli. Participants are told to use semantic categories in the formulation of responses or to judge semantic category membership (Giffard et al., 2001).

4.3.4 Implicit/Explicit and Direct/Indirect Semantic Priming

In terms of explicit semantic access, three studies have reported intact accuracy and RT priming in SZ using directly related stimuli (Kiang, Christensen, & Zipursky, 2011; Kreher et al., 2009; Moelter et al., 2005). Kraut et al. (2002) created an indirect explicit task that required participants to determine whether two words, for example HONEY-STINGS, evoked the idea of another concept (BEE). Assaf et al. (2007) used this task in a SZ sample and found that participants were slower than controls to categorise related pairs correctly and incorrectly categorised unrelated pairs as related more often. Thus, the literature to date in SZ has suggested normal explicit processing with direct stimuli, and abnormal function when using indirect stimuli.

In addition, one study has used the same implicit and explicit tasks as those used in the current study to examine healthy controls under the influence of ketamine (a psychomimetic drug) (Neill et al., 2011). The results found that ketamine led to increased indirect implicit priming as per SZ (Pomarol-

Clotet et al., 2008; Rossell & Stefanovic, 2007), and increased errors in direct implicit priming. The explicit results were in line with SZ findings with normal direct processing and more errors when processing indirectly related pairs (Kiang et al., 2011; Kreher et al., 2009; Lecardeur et al., 2007).

To examine the semantic processing of direct and indirect pairs both implicitly and explicitly, four tasks were employed. Two implicit tasks (direct and indirect) were created for this experiment. Both tasks included short presentation times and a distractor task. Regarding the explicit condition, Krauts (2002) indirect task (known as the 'Objects' task) was used. A direct task (named the 'Association' task) was created based on the format of Kraut's indirect task. The inclusion of the four tasks allows for a balanced design and will provide a full picture of semantic processing performance in SZ.

This is the first study to compare the same SZ group across both implicit and explicit semantic tasks using directly and indirectly related pairs. In terms of the implicit task performance, it is hypothesised that the SZ group will demonstrate increased indirect priming in comparison to controls. No specific hypothesis is made for the implicit direct task due to the mixed results in the literature. For the explicit tasks, it is hypothesised that on the indirect task, SZ participant performance will be associated with abnormalities in both RT and error data as found in Assaf's study (2007). The direct 'Association' task has not been used in SZ but it is predicted that performance on this task will not differ between groups. This is because the task requires recognising more simple direct relationships with instructions and a longer response window for information processing (2.7 seconds). Finally, because of the findings of the meta-analysis by Pomarol-Clotet et al. (2008) that suggested greater

indirect priming in those with thought disorder, it is hypothesised that there will be a positive correlation between degree of priming and level of thought disorder.

4.4 Methods

4.4.1 Participants

Eighteen SZ participants were outpatients who responded to advertising in supported accommodation and community mental health services; and four inpatients at the Alfred Hospital Melbourne who were willing to participate with their consulting psychiatrist's permission. Diagnosis and symptom profile was investigated using the Structured Clinical Interview Diagnostic (SCID) (First et al., 1997) and current symptoms were evaluated using the Positive and Negative Symptoms Schedule (PANSS) (Kay, Fiszbein, & Opler, 1987). All patients needed to score >40 but <80 on the total PANSS score as well as having a clinical diagnoses of schizophrenia to be accepted into the study (Leucht et al., 2005). This ensured all patients were mild to moderately unwell at the time of testing, but not severe, to ensure that they were able to provide consent and understand all study instructions. TD was additionally rated throughout the SCID using the Thought Language and Communication scale (TLC) (Andreasen, 1979). Twenty-one healthy controls were recruited from advertisements around the Alfred Hospital and Monash University. They were screened for psychiatric illness using the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) and were excluded if they had any history of psychiatric illness.

4.4.2 Implicit Priming Tasks

The stimuli for direct and indirect implicit priming tasks included 60 related word-word pairs and 30 word-pseudo-word pairs. From these stimuli, two word lists were created (A and B). In version

A, 30 of the 60 word–word pairs remained related, while the other 30 pairs were re-arranged so that they now formed unrelated pairs. In version B, these relationships were counterbalanced, so that related pairs from list A were randomly re-assigned to create unrelated pairs, and the unrelated pairs were arranged back into their related word pairing. Both lists A and B also included 30 pseudo-word pairs. A short SOA (250msec) was used as this is the length of time commonly adopted by studies investigating 'unconscious' processing (Rossell & Stefanovic, 2007). Primes were presented for 200msec, followed by a 50msec inter-stimulus interval. The target was presented for 200msec and with an additional 2000ms response window. Participants were able to respond from the time the target appeared on screen. The lists were matched on number of letters, syllables and phonemes in each word, frequency, concreteness and imagability. Pseudo-words were pronounceable and legally spelled letter strings (e.g. pont) and were selected from the ARC pseudo-word database (Rastle et al., 2002). These tasks can be considered implicit because participants are not told that the pairs they are responding to may be related. Instead, they are given a distracter lexical decision task. They are told to press one button if the second word of the pair is a real word and another button if it is a pseudo-word (making this a lexical decision task).

4.4.2.1 Direct Priming Task

Directly related word pairs used in this study included those with a direct semantic (i.e. SCOTCH-WHISKEY) or associative (i.e. DART-BOARD) relationship. All pairs had an association value > 10 in the Edinburgh Word Association Thesaurus (EAT: http://www.eat.rl.acu.au); the mean association value for the stimuli was 32.36.

4.4.2.2 Indirect Priming Task

Indirectly related word pairs describe those words related via their mutual association with a third concept. For example, LION-STRIPES are indirectly related via their association with TIGER. The EAT was used to ensure that there was no direct association between these pairs (all pairs <10).

4.4.3 Explicit Priming Tasks

The explicit tasks were adapted from the Object task used by Assaf (2006). They are explicit because participants are directed to consider the semantic relationships of the pairs. In both explicit tasks, participants responded to 32 pairs of words. Both the prime and target at the same time (prime above target). The stimuli remained on screen for 2.7 seconds and participants were given a further 1.5 seconds after stimuli disappeared from the screen to respond.

4.4.3.1 Association Task (direct)

In the Association Task, participants were presented with pairs of words, and were asked to determine whether the pairs were associated with one another (e.g. CAT and DOG are related because they are pets) or not (CAT-PENCIL).

4.4.3.2 Object Task (indirect)

In the Object Task, participants were presented with pairs of words, and were asked to judge whether the two words were connected via an association with a third word (e.g. HONEY and STING were presented and are connected via their association with BEE) or not (HONEY-BANGLE).

4.4.3.3 Procedure

For all tasks participants used a two button press, and were asked to respond as quickly and accurately as possible. Participants were given practice examples with feedback before each task. Accuracy and RT data were used for analysis. The implicit indirect task was always completed first.

4.3.4 Data Preparation

4.4.4.1 Reaction Time

For each participant, all RT's more than two standard deviations from the mean for that group were replaced with the value two SD's from the mean; this removed anticipatory responses <~100msec and delayed responses >~2000msec (Collins, 1999; Collins, 2002). This rule was applied for <5% of the data. RT priming for both the implicit and explicit tasks was calculated simply as 'unrelated – related' as there was no significant slowing in the SZ group.

4.4.4.2 Accuracy

Participants with more than 30% errors (false positives and negatives) were excluded (Cohen, 1988). No participants were excluded on this basis. Accuracy priming for both the implicit and explicit tasks was calculated as: mean number of errors for unrelated pairs – mean number of errors for related pairs.

4.4.5 Statistical analysis

Groups were compared using t-tests on salient demographic and clinical variables to determine whether there were any differences that needed to be controlled for. Priming research suggests that

demographic variables like age (Laver & Burke, 1993), length of illness (Maher et al., 1996), medication (Barch et al., 1996), and total years of education (Spitzer, Braun, Hermle, & Maier, 1993) specifically can impact on semantic priming. As such, these variables were correlated with the related and unrelated task variables from the four priming tasks. Correlations were also run between thought disorder and the implicit and explicit tasks to determine whether this symptom showed an association with priming. These correlations are presented where relevant throughout the results section.

Although the implicit and explicit tasks were designed to be as similar as possible a full factorial model 2 group (SZ, control) x 2 relatedness (related, unrelated) x 2 semantic priming types (direct, indirect) x 2 memory levels (implicit, explicit) was not possible due to procedural differences across the tasks in terms of stimuli presentation times, SOA and response windows. However, it was possible to perform 2 group x 2 relatedness x 2 semantic priming types repeated measures analysis of variance at each memory level for RT and accuracy data. Post-hoc ANOVAs and t-tests were used to address specific hypotheses. Priming was calculated as unrelated RT – related RT. Post-hoc tests were only conducted if interactions included group effects and all post-hoc tests were Bonferroni corrected.

SZ is associated with slowed information processing (Knowles, David, & Reichenberg, 2010) and there is evidence that this magnifies priming effects artificially (Chapman et al., 1994). This is based on the finding that there is a positive correlation between raw latency difference scores and slowed processing. One method used to correct for this slowing is to calculate priming as a percentage using the following formula (1- related/unrelated)*100 (Spitzer, Braun, Hermle, & Maier, 1993). T-tests were run on the following data and percentage priming calculated for those tasks associated with slow RT in the SZ group.

4.5 Results

Assumptions of Normality

After we had trimmed the data in the current study assumptions of normality, linearity, and multicollinearity were met. The Box's M was found to be non-significant indicating that the homogeneity of variance-convariance assumption had been satisfied

Demographic Correlations

The study groups were matched for IQ and years of education, but differences were identified in age (see Table 1). Correlations showed no significant relationships between raw RTs (r=0.29, p=0.07) or error data (r=-0.13, p=0.44), to age; therefore age was not used as a covariate. Additionally, there were no significant correlations between RT and errors with thought disorder or medication dose which was calculated from Chlorpromazine equivalents (Lambert).

General Slowing

There was no significant difference between the SZ (M=689 ± 113) and control group (650 ± 81) on the implicit tasks (t (36) = -1.26, p=0.22, *d*= 0.39). The SZ group was slower (M=1464 ± 246) than controls (M=1272 ± 145) on the explicit tasks (t (38) = -2.99, p=0.01, *d*=0.95).

4.5.1 Implicit Tasks

4.5.1.2 Reaction Time Data

The repeated measures ANOVA with RT data found no main effects and no two way interactions involving group. There was a three way interaction between prime type x relatedness x

group (F (1, 36) =4.11, p=0.05) (see Table 4.1 for raw RT and error data). While the interaction is only equal to significance, post hoc analysis was conducted because an a-priori prediction and specific hypothesis were made with regard to differences in priming on the indirect task between controls and schizophrenia participants. These post hoc analyses were conducted using independent samples t-tests on the priming scores. Alpha level was set to 0.01 to account for multiple comparisons. There was significantly more priming on the direct task for the healthy controls (M=57msec ± 49) compared to SZ (M=12msec ± 45; t (38) = 3.06, p<0.01, *d*= 0.96). There were no group differences in degree of priming for the indirect task between healthy controls (M= -23msec ± 46) and SZ (M= -9msec ± 42, t (37) = -1.02, p=0.31, *d*= -0.32). To further understand the significant group differences on the direct task, paired samples t-tests were conducted. Results showed significant priming for the controls (t (20) = -5.4, p<0.001, *d*= -0.65) but not for the SZ group (t (18) = -1.21, p=0.24, *d*= -0.11) (see Figure 4.1). The finding of reduced direct priming at a short SOA has been linked to chronic SZ (Minzenberg et al., 2002). Correlations between length of illness and raw RT to related and unrelated pairs on the direct task demonstrated a significant relationship between related (r= 0.51, n=18, p=0.03, *d*=1.18) and unrelated pairs (r=0.5, n=18, p=0.05, *d*=1.15) with length of illness on the implicit direct task. After correcting for multiple comparisons, these findings are reduced to trend level. Given the support from previous literature and the large effect sizes however, this relationship will still be considered in the interpretation of the results.

Table 4.1 *Implicit Reaction Time and Accuracy*

Implicit Task	Group (N)	Relatedness	% Correct Mean (SD)	RT in msec Mean (SD)	RT Priming Score Raw (R-U) (SD)
Direct	Controls (21)	Related	99 (2)	621 (81)	58 (49)*
		Unrelated	96 (4)	679 (97)	

	SZ (18)	Related	96 (5)	681 (115)	12 (45)
		Unrelated	94 (7)	693 (98)	
Indirect	Controls (20)	Related	97 (3)	661 (91)	-23 (46)*
		Unrelated	97 (3)	637 (90)	
	SZ (19)	Related	96 (5)	709 (142)	-9 (43)
		Unrelated	96 (7)	700 (126)	

*p<0.05

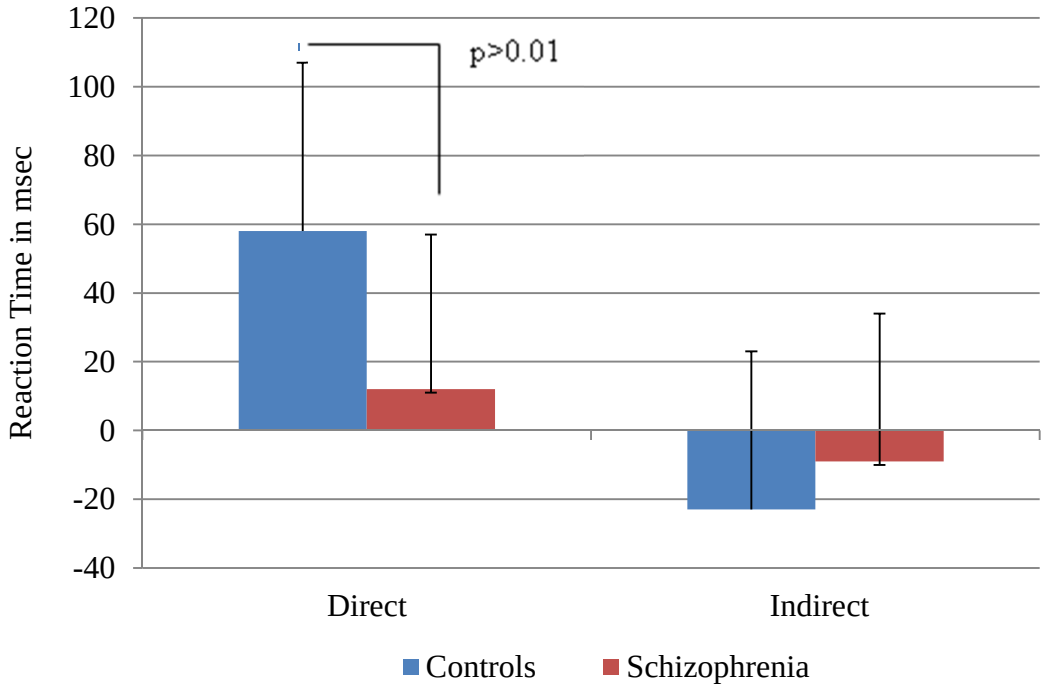

Figure 4.1 Implicit Semantic Priming

4.5.1.3 Error Data

Repeated measures ANOVA with error data found no main effects. There was no three way interaction and no interactions with group.

4.5.2 Explicit Tasks

4.5.2.1 Reaction Time Data

Repeated measures ANOVA showed significant main effects for prime type (F (1, 36) =24.2, p<0.001, *d*= -0.84), with faster RT to the direct (M=1246msec ± 216) than the indirect pairs (M=1457msec ± 283); and for relatedness (F (1, 36) =43.37, p<0.001, *d*=-0.93), with faster RT to related (M=1248 ±178) than unrelated pairs (M=1454msec ±259). Finally, there was a main effect for group (F (1, 36) = 6.80, p=0.01, *d*= 0.83) with slower RT in the SZ group (M= 1429msec ± 221) compared to controls (M=1273msec ± 145). There were no two or three way interactions.

Percentage priming was calculated due to the slowing found in the SZ group across the explicit tasks (see Table 4.2). Independent t-tests showed that the SZ group (M=12% ± 16) were not significantly different from controls (M=9% ± 13) on the Association task (t (37) = -0.61, p=0.54, *d*= 0.21); or on the Objects task; SZ (M=18% ± 14), controls (M=12% ± 16;t (37) = -2, p=0.23, *d*= 0.4) (see Figure 2).

Table 4.2 *Explicit Reaction Time and Accuracy*

Explicit Task	Group (N)	Relatedness	% Correct Mean (SD)	RT in msec Mean (SD)	RT Priming Score Raw (Unrelated-Related) (SD)	% Priming (1- related/ unrelated)*100 (SD)
Association	Controls (21)	Related	96 (4)	1082(138)	124 (208)	9% (13)
(Direct)		Unrelated	97 (4)	1206 (154)		
	SZ (19)	Related	93 (9)	1238 (217)	214 (288)	12% (16)

		Unrelated	94 (7)	1452 (350)		
Object	Controls (20)	Related	92 (6)	1307 (315)	185 (240)	12% (16)
(Indirect)		Unrelated	96 (5)	1492 (276)		
	SZ (19)	Related	81 (19)	1381 (211)	342 (326)	17% (14)
		Unrelated	83 (23)	1723 (409)		

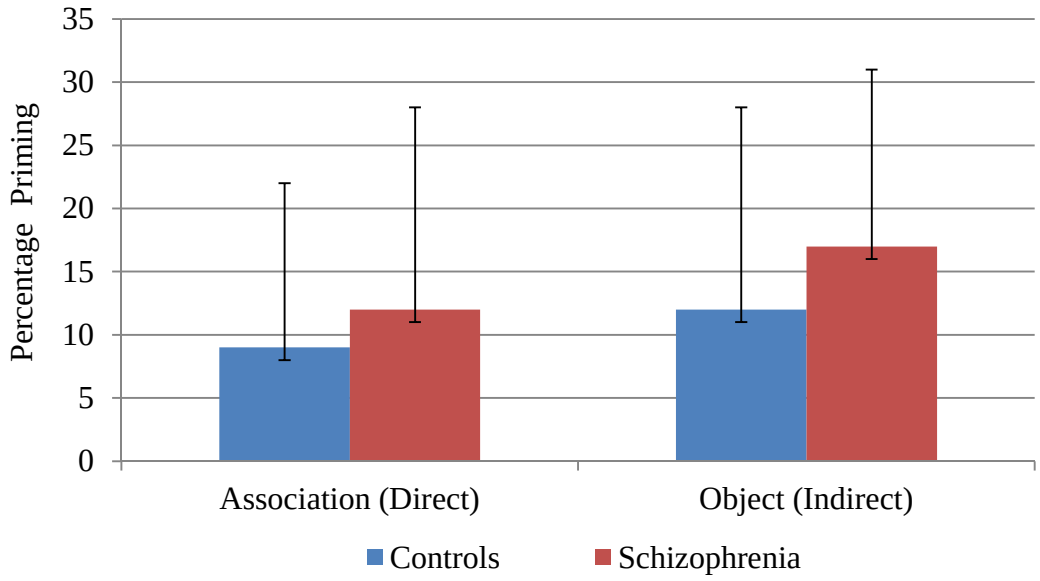

Figure 4.2 Explicit Semantic Priming

4.5.2.2 Error Data

Repeated measures ANOVAs found a main effect for prime type (F (1, 44) =12.71, p<0.001, *d*= 0.74) with greater accuracy for direct (M=94% ± 6) than indirect pairs (M=87% ± 12). There was also a main effect for group (F (1, 44) = 11.09, p<0.001, *d*= -0.83) with reduced accuracy in the SZ group (M=88% ± 10) compared to the controls (M=94% ±2). There were no two or three way interactions.

4.6 Discussion

The SZ group demonstrated different patterns of performance across implicit and explicit tasks. Explicit performance was characterised by general deficits across tasks in RT and accuracy in spite of the provision of extra processing time and structure (provided by instructions and a longer response window than that provided by implicit tasks). Despite these deficits, priming was elicited in the SZ group on both tasks to a similar degree to that seen in controls. On the implicit tasks the only group difference was an absence of priming for the direct task in SZ in the face of intact RT and accuracy performance generally. In terms of overall RT and error performance, these findings confirm general observations regarding memory performance in SZ as characterised by intact implicit and deficient explicit performance (Clare et al., 1993; Perry, Light, Davis, & Braff, 2000). Priming performance, on the other hand, was associated with the opposite pattern with intact explicit and impaired implicit priming.

4.6.1 Implicit Results

In the SZ group, priming was reduced on the direct implicit task. There is literature to support reduced direct priming in SZ (Aloia et al., 1998; Ober et al., 1997; Rossell & David, 2000); this pattern of performance has been attributed to various factors including the use of association only pairs (Ober et al., 1997), high levels of thought disorder (Aloia et al., 1998; Besche et al., 1997; Passerieux et al., 1997) and emotional content of stimuli (Rossell & David, 2000). The current study included both category and association pairs that had little or no emotional salience in a low thought disorder sample. Medication did not correlate with direct priming. However, there was a relationship (albeit at trend level) between length of illness and RT to related and unrelated pairs from the direct task; suggesting

that reduced direct priming relates to the SZ groups length of illness. This relationship has also been reported in previous literature (Maher et al., 1996), amongst a SZ group with an average length of illness of 15 years. The current samples length of illness was longer again with an average of 18 years since diagnosis.

There were no group differences in degree of priming on the indirect task between groups. Both group demonstrated negative priming (slower RT to related than unrelated pairs). This finding is usually reported in response to studies designed to assess post-lexical strategy use. This goes against the hypothesis of enhanced indirect priming in SZ. It is likely that the lack of indirect priming in the SZ group stems, at least partly, from the length of illness of the current sample and/or may be the result of their low levels of thought disorder (see Table 1). Research suggests that hyperpriming is most convincingly elicited in high thought disorder groups (Pomarol-Clotet et al., 2008); and studies comparing high to low thought disordered groups have reported no significant indirect priming in their low thought disordered group (Spitzer, Braun, Hermle, & Maier, 1993).

4.6.2 Explicit Results

There was significant priming found for both groups across both explicit tasks. The SZ group demonstrated slower RT and more errors overall. There was no evidence of a specific deficit on the direct Association task. This finding was predicted based on the simple and structured nature of this task. In terms of the indirect Objects task, these findings broadly support the work of Assaf (2006). They found that patients falsely identified unrelated pairs as related and were slower to respond to related pairs. The findings of the current study indicated a more general impairment on the explicit tasks as there were no interaction effects. In terms of priming performance, the provision of extra

processing time and structure may have ameliorated some of the associated cognitive problems that reduce priming in implicit conditions.

These results differ to the ketamine study that utilised exactly the same tasks (Neill et al., 2011). This finding may be explained in terms of length of illness. Research using ketamine to model psychosis report that this drug induced psychosis is a better model for early rather than long term/chronic psychosis (Jentsch, 1999; Morgan & Curran, 2006).

Overall, these results provide a picture which supports both the traditional view on SZ performance across implicit and explicit memory tasks, (i.e, implicit performance is intact whilst explicit performance is impaired) whilst still highlighting the special case of abnormal semantic priming effects. This paper provides clarity to a body of literature which, until now, has had to draw conclusions about semantic processing deficits by comparing studies made up of different schizophrenia participants with varied demographic and symptom profiles. Finally, the finding of no enhanced indirect priming (and in fact negative priming) is best explained by low levels of thought disorder and a considerable length of illness. These findings are made more significant by the fact that they were found in the same group, avoiding the confounding variables of different medications, symptom profiles, age, and length of illness.

4.6.3 Limitations

Future research should consider using the same stimuli in the implicit and explicit tasks so that the relationships between the specific pairs can be examined across the two conditions. Sample size is also a limitation of the current study. Further, it would be beneficial to recruit early episode SZ

participants, and include those with high levels of thought disorder. This would help to clarify some of the confounding factors that affected the implicit priming results.

4.6.4 Conclusion

This study is the first to examine implicit and explicit semantic access in the same SZ sample. The data suggest that chronic SZ is associated with impairments in implicit direct semantic processing. There is also evidence that explicit processing, whilst associated with increased errors and slower performance, can boost the processing of semantic relationships.

CHAPTER 5. COMPARISON OF ANALOGUE PERFORMANCE TO SCHIZOPHRENIA

DECLARATION FOR THESIS CHAPTER 5

Declaration by candidate:

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, data collection, data analysis and writing of the chapter.	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Susan Rossell	Supervisor of Erica Neill's PhD. Provided assistance in data analysis and proof reading of the chapter

Candidates Signature: [redacted] **Date: 14/01/13**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from 2009

Susan Rossell Signature: [redacted] **Date: 14/01/13**

5.1 Chapter Guide

This chapter includes a comparison of implicit and explicit semantic function across the participant groups examined in Chapters Two, Three and Four. This comparison chapter has not been submitted as an article at this stage.

5.2 Introduction

In Chapters Two and Three, two analogue models of schizophrenia were examined in comparison to a control condition/group on four semantic memory tasks. In those chapters, inferences were made as to the accuracy with which each model matched the patterns of performance reported in the schizophrenia literature. In Chapter Four, a schizophrenia group were compared to controls on the same four semantic tasks. In the current chapter, each analogue model is compared directly to a schizophrenia group so the validity of each model can be assessed directly.

With regards to the implicit semantic priming tasks, the four groups cannot be directly compared. This was because the presentation lengths of the stimuli within the implicit semantic priming tasks were extended for the ketamine group. This was a precautionary measure as the effects of ketamine are known to interfere with processing speed (Harborne, Watson, Healy, & Groves, 1996). There is very little research examining whether slowed processing speed impacts on semantic performance specifically. Of the literature available, results are mixed; some research shows that ketamine does not slow RT in priming tasks (Morgan, Rossell, et al., 2006; Stefanovic et al., 2009), whilst others find that general semantic processing is slowed (Curran & Monaghan, 2001; Morgan et al., 2004) (although, the 2004 study found this to be at trend level). In Chapter Two, the ketamine results were published with regards to a long SOA of 950msec which provided participants with an extended period of time to process pairs. A clearer distinction between implicit and explicit processing is provided by a shorter SOA (see section 1.2.3 of Chapter One for more detail regarding implicit vs. explicit access). Given that there was a risk that semantic processing would be slowed, and given the high dose administered for the ketamine study, it was decided that the implicit priming task SOA should be shorter that 950msec but not so short that the drug affected participants could not complete it.

It was therefore decided that the short SOA for this group would be set at 450msec. In a review of hyper-priming to indirect pairs in schizophrenia, Rossell noted that for an SOA to be regarded as automatic (or implicit) it is should be less than 500msec (2007). It was therefore determined that an SOA of 450msec would still sit within this range whilst providing ample processing time for the ketamine affected participants. While the priming study by Morgan (2006) did find intact priming for direct pairs using an SOA of 250msec, the ketamine dosing is not directly comparable and at the time of designing the study, it was determined that our blood ketamine levels might end up being higher than those found in Morgan's study (see Chapter Two for more details on dosing).

Half the schizophrenia participants recruited for this thesis completed a priming task at a 450msec SOA (N=21 schizophrenia participants) as did half of the healthy control group recruited (N= 21 control participants). For the schizotypy study, the short SOA was set to 250msec as this is a healthy group who are unlikely to be affected by slowed processing speed. The other half of the schizophrenia group recruited and a matched group of healthy controls completed the same 250msec priming tasks so that direct comparisons with the schizotypy group could be made. The reason for using the 250msec SOA, instead of simply relying on a uniform SOA of 450msec throughout the thesis, stems from the Rossell review (2007) which described most schizophrenia priming studies finding hyperpriming employed an SOAbetween 200 and 260msec. This shorter SOA also helps to ensure that the task is as implicit as possible. In sum, in the current chapter there will be two sets of schizophrenia comparisons.

COMPARISON A: comparisons were made between the healthy controls under the influence of ketamine, a group of separate healthy controls and a schizophrenia group at 450msec.

COMPARISON B: The second set of comparisons was made between a high schizotypy group, a group of low schizotypy participants and a schizophrenia group at 250msec.

Before the analogue hypotheses can be proposed, hypotheses regarding schizophrenia performance must be made. Schizophrenia performance on direct implicit priming tasks are mixed. Some research finds increased priming (Chenery et al., 2004; Rossell & David, 2006; Weisbrod et al., 1998), some decreased (Aloia et al., 1998; Besche et al., 1997; Ober et al., 1997; Passerieux et al., 1997; Rossell & David, 2000) and some normal (Chapin et al., 1992; Minzenberg et al., 2003; Quelen et al., 2005; Spitzer, Braun, Hermle, & Maier, 1993; Surguladze et al., 2002). As such, no specific hypotheses are made in regards to performance on this task. Schizophrenia is associated with hyperpriming in response to implicit indirect pairs (Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007). This finding is particularly strong amongst those with thought disorder. As such, it is predicted that implicit indirect priming will by enhanced generally, but more specifically so in thought disorder. In terms of explicit tasks, direct semantic memory tasks are associated with mixed findings (Bonner-Jackson & Barch, 2011; Whittaker et al., 2001). These tasks are reasonably different from the task designed and used in this thesis. Given that other explicit task results are mixed, and given that this task has not been used in schizophrenia before, no specific hypotheses are made. In terms of the indirect task, this task was adopted from a study which administered this test to a schizophrenia sample (Assaf et al., 2006). These authors found that schizophrenia was associated with abnormal performance. As such, it is hypothesised that the schizophrenia group will demonstrate abnormal performance on this task.

COMPARISON A: The ketamine results in Chapter Two were discussed only in reference to long SOAs. With regards to the current investigation of short SOA performance, there are two previous studies that have examined priming in ketamine with a short or no SOA (Morgan, Rossell, et al., 2006; Stefanovic et al., 2009). Morgan found that at a short SOA of 250msec using directly related pairs; there were no group differences in performance at a ketamine dose theoretically similar to the one used in the current study. Stefanovic found that, with directly related pairs, their placebo group demonstrated greater priming on a strategic task (SOA 750msec, relatedness proportion (RP) = 60%) than on an automatic task (SOA of 250msec, RP =20%) whilst the ketamine group did not differ in degree of priming across the two tasks. There were no group differences in performance on priming tasks when they were made up of indirectly related pairs (SOA = 0, RP = 33.3%) (RP's for both of these studies were calculated using the method described by Minzenberg (2003): (related x 100)/total real words).

In predicting ketamine performance, a number of different approaches may be considered: (1) Previous ketamine results, (2) ketamine as an analogue for schizophrenia, (3) the access/storage debate and (4) the implicit/explicit literature.

Approach (1): It is difficult to compare the current study to these previous ketamine studies due to design differences. Whilst the study by Morgan uses a similar dosing method, the SOA and RP are different. Stefanovic used a range of SOAs and RP's but none match the current study. Further, there are only two papers for the purposes of comparison. Given that ketamine is supposed to mimic schizophrenia effects and given the discrepant findings in the ketamine literature, hypotheses put forward are not based on this previous literature but on the schizophrenia literature.

Approach (2): If ketamine models schizophrenia deficits, then it is predicted that under the influence of ketamine, participants will demonstrate increased indirect priming (Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007). No specific predictions are made with regards to the direct priming task as the schizophrenia literature is mixed in this regard (Chenery et al., 2004; Quelen et al., 2005; Rossell & David, 2000). Specific hypotheses for performance on the explicit direct task are also difficult because this task has not been used in schizophrenia, before and because the literature that examines similar explicit, direct semantic function is mixed. There is one study examining explicit indirect priming which found abnormalities in schizophrenia performance. Given that the same task is used for the current thesis, it is predicted that performance on this task will be abnormal under ketamine.

Approach (3) Although the design of the implicit and explicit tasks do not allow for an in-depth examination of the access/storage debate, there is some scope to make hypotheses about ketamine performance with this in mind (for a description and discussion of the access/storage debate refer back to section 1.3.4.3 in Chapter One). If ketamine does impair semantic performance, it is likely to do so by impairing semantic access rather than storage as a single dose of ketamine is unlikely to change the structure of this memory system. If ketamine does impair semantic access, then implicit performance will be normal for direct pairs. There has been no investigation of the effect of an access problem on indirect priming. Based on Spitzer and colleagues (1993) proposition that hyperpriming to indirect pairs represents abnormal access, it is hypothesised that there will be hyperpriming to indirect pairs. It is further predicted that the instructions associated with the explicit tasks will compensate of any access

problems elicited by ketamine. Therefore, it is expected that ketamine and control performance will be the same across the explicit tasks.

Approach (4) The implicit literature in schizophrenia is inconsistent with regards to direct performance but suggests that schizophrenia performance will be characterised by abnormal performance on the indirect implicit task as predicted by approaches (2) and (3). The explicit literature is also mixed, and no clear predictions can be made regarding direct performance. Indirect performance has been examined in only one study. The results of this study found abnormalities in indirect performance. Given that the same task is used for the current thesis, it is predicted that explicit performance will be abnormal on the indirect explicit task.

COMPARISON B: In terms of schizotypy, the literature is mixed with regards to short SOA priming results (Johnston et al., 2008; Morgan, Bedford, et al., 2006; Pizzagalli et al., 2001). Johnston and colleagues (2008) included a direct and indirect task with an SOA of 250msec and a 50% relatedness proportion (all RP's reported for these studies have been re-calculated using the method described by Minzenberg (2002) so that studies are more comparable). The authors found that there was a positive correlation between the cognitive disorganisation scale of the O-LIFE and the indirect priming task. Another study examined high and low frequency priming in schizotypy (measured using the O-LIFE) at an SOA of 200msec and a relatedness proportion of 50% (Morgan, Bedford, et al., 2006). The main finding was that the high schizotypy group showed a trend to demonstrating less priming generally with directly related pairs. A study by Pizzagalli and colleagues (2001) combined direct and indirect pairs into the same task and examined lateralised priming (SOA=0, relatedness

proportion 66%). They found that those scoring high on a magical ideation scale demonstrated high levels of indirect priming in the right hemisphere and less indirect priming in the left hemisphere.

The same four approaches can be used to make predictions about schizotypy performance.

Approach (1) Similar to the ketamine literature, the schizotypy literature is plagued by differences in study design. Despite these differences, two of the three studies examined found that high schizotypy was associated with increased indirect priming (specifically in the right hemisphere in the Pizzagalli study). As such, it is predicted that high schizotypy will be associated with increased indirect priming at the implicit level. Once again, direct implicit findings are mixed so no specific hypotheses are made. There have been no studies examining schizotypy performance in relation to explicit semantic tasks. As such, no predictions will be made regarding explicit performance using this approach.

Approach (2) The schizophrenia results have already been discussed in the examination of the second approach for ketamine. As such, it is predicted that high schizotypy will be associated with increased indirect priming implicitly and abnormal indirect priming explicitly. More generally, if schizotypy is a good model for schizophrenia, this group will demonstrated a milder version of the schizophrenia performance pattern.

Approach (3) If schizophrenia is on a continuum with schizotypy representing a milder form of psychosis pathology, then some storage deficits may be found. A storage pattern of deficit on implicit tasks may be characterised by mild hyperpriming (mild because they are a healthy group) on the direct

task and reduced indirect priming. This has not been explicitly examined in schizophrenia but is inferred from the criteria offered by Warrington and Shallice (1975) and the findings of Rossell and David (2006) (see Chapter One, Table 1.6). In terms of explicit performance, a storage deficit should not be alleviated by instruction. As such, indirect performance should be abnormal. The performance on the direct task will likely be intact given that this is a healthy group and a significant degree of impairment would need to be present to impair commonly used direct pairs.

Approach (4) As with the suggestions from the ketamine comparison, it is predicted that indirect performance will be abnormal both implicitly and explicitly.

Some past literature has suggested that schizophrenia is associated with a semantic storage deficits (Rossell & David, 2006). If this is indeed accurate, and if schizotypy is on a continuum with schizophrenia, there may be some deficits present in explicit semantic processing, albeit milder than those found in schizophrenia. Given that the explicit direct task provides instruction and the relationships are direct however, it is proposed that deficits will not be detected on this task in schizotypy when compared to the schizophrenia cohort. There is data on an explicit indirect priming task in the schizophrenia literature (Assaf et al., 2006). Results have shown that, at trend level, schizophrenia was associated with a slowing in categorising related pairs as related and made more errors in falsely categorising unrelated pairs as related. As such, it is hypothesised that the schizotypy group may demonstrate mild difficulties on the explicit, indirect semantic task; thus their performance will fall between the schizophrenia cohort and the healthy controls.

5.3 Data analysis

For each of the comparisons presented below, the following analyses were performed:

5.3.1 Demographic Variables

The participant groups were compared on a number of demographic variables (age, total years of education and WTAR) (premorbid language IQ estimate) previously associated with priming performance so that in later analyses, group differences on any of these variables can be controlled for statistically.

5.3.2 Slowed Processing Speed in Experimental Groups

In addition, there is the possibility of slowing in the schizophrenia group. This problem was not specifically examined in the schizotypy or ketamine chapters, and so it will be explored in the data analysis for this chapter. To determine if slowing was a problem for any of the experimental groups, overall RT's were examined for each of the four tasks. One-way ANOVAs were run separately for the 250msec and 450msec groups.

5.3.3 Comparisons between groups

Repeated measures ANOVA will be run to investigate the relationships between groups (Comparison A: Ketamine, schizophrenia, controls; Comparison B: Schizotypy, schizophrenia, controls), relatedness (related and unrelated pairs) and pair type (direct and indirect pairs) separately for the implicit and explicit tasks. Interactions and specific hypotheses were examined using follow-up one way ANOVAs and t-tests. Paired samples t-tests were run to determine whether priming had occurred in each of the conditions even in cases where specific hypotheses were not made. This was to provide a fuller picture of priming function across the experimental groups.

5.4 Results

5.4.1 Comparisons between participants across SOA's

Firstly, the fact that the participant group completing the alternative SOAs were well-matched on demographic and symptom data will be demonstrated. This will be done by comparing the healthy control group who completed the 250msec implicit tasks to those healthy controls who completed the 450msec implicit tasks. The same analysis will be completed for the schizophrenia groups. T-tests will be run between participants on each of the relevant variables. The p value is adjusted to 0.01 to control for multiple comparisons.

5.4.2 Comparison A: Schizotypy, schizophrenia, controls

5.4.2.1 Demographics: Within Groups

The control groups were well matched on relevant demographic variables across the SOA conditions. The schizophrenia groups did not differ in relevant demographic variables across the 250 and 450msec conditions (see Tables 5.1 and 5.2).

Table 5.1 T-test *Comparisons Between Healthy Controls at the Two SOAs*

	Healthy Controls (250msec)	Healthy Controls (450msec)	t value	p value
Age (years)	30.38 (9.84)	36.32 (14.53)	-1.53	0.15
Education (years)	15.71 (2.10)	16.74 (2.96)	-0.85	0.21
WTAR IQ	102.00 (7.89)	104.56 (10.62)	-0.89	0.40

Table 5.2 T-test *Comparisons Between Schizophrenia Participants at the Two SOAs*

	Schizophrenia (250msec)	Schizophrenia (450msec)	t value	p value
Age (years)	40.00 (12.16)	40.50 (9.51)	0.14	0.89
Education (years)	14.50 (3.96)	15.62 (4.10)	0.87	0.39
WTAR IQ	101.42 (13.85)	97.20 (15.56)	-0.89	0.38
TLC (total)	3.42 (9.96)	3.80 (6.04)	0.15	0.89
PANSS (Positive)	14.58 (3.96)	16.10 (4.97)	1.05	0.30
PANSS (Negative)	10.05 (1.62)	12.20 (4.18)	2.10	0.04
PANSS (General)	25.63 (4.90)	28.90 (8.66)	1.44	0.16
PANSS (total)	50.26 (8.67)	57.20 (15.06)	1.75	0.16
Length of illness	17.44 (11.44)	17.50 (9.24)	0.02	0.99
CPZ mean dosage	469.88 (348.65)	511.75 (368.95)	0.35	0.73

5.4.2.2 Demographics: Between Groups

There were significant group differences in age ($F(2, 54) = 13.79$, $p<0.001$), but not for years of education ($F(2, 50) = 7.75$, $p=0.51$) or WTAR scaled score ($F(2, 54) = 2.28$, $p=0.11$). The age difference stemmed from the fact that the schizophrenia group ($M=40 \pm 12.16$) were significantly older than the schizotypy ($M=23.94 \pm 3.75$, $p<0.001$) and the control groups ($M=30.38 \pm 9.84$, $p=0.01$) (see Table 5.3). These variables were correlated with priming for all four semantic tasks to determine whether they were contributing to priming results. Correlational analysis demonstrated that there were no relationships between semantic performance and age (see Table 5.4). As such, no covariates were entered into the following analyses.

Table 5.3 *Comparison A: Demographics*

250msec	Schizophrenia	Schizotypy	Controls
Male/Female	10/9	8/10	6/15
Age (years)	40.00 (12.16)	23.94 (3.75)	30.38 (9.84)
Education (years)	14.50 (3.96)	15.42 (2.12)	15.71 (2.10)
WTAR IQ	101.42 (13.85)	107.89 (7.55)	102.00 (7.89)
TLC (total)	3.42 (9.96)		
PANSS (Positive)	14.58 (3.96)		
PANSS (Negative)	10.05 (1.62)		
PANSS (General)	25.63 (4.90)		
PANSS (total)	50.26 (8.67)		
Length of illness	17.44 (11.44)		
CPZ mean dosage	469.88 (348.65)		

5.4.2.3 Slowed Processing Speed

There were no significant group differences in overall RT to the implicit tasks ($F(2, 53) = 1.95$, $p=0.15$). There was a group difference on the explicit tasks ($F(2, 53) = 3.46$, $p=0.04$). The schizophrenia group were significantly slower ($M=1429.4 \pm 220.7$) than the healthy controls ($M=1272.9 \pm 145.1$, $p=0.03$). There was no RT difference between schizophrenia and schizotypy ($M= 1334.8 \pm 181.9$, $p=0.28$) or between schizotypy and controls ($p=0.56$). As a result of the slower overall RT of the schizophrenia group on the explicit tasks, follow up ANOVA's looking specifically at group effects in RT to the explicit tasks were run using percentage priming (the justification for using percentage priming is discussed in section 1.4.9 of Chapter One).

Table 5.4 *Comparison A: Correlations Between Demographics and Semantic Tasks*

% Priming 250msec		Controls			Schizotypy			Schizophrenia		
		Age	Yrs. Educ	WTAR Scaled	Age	Yrs. Educ	WTAR Scaled	Age	Yrs. Educ	WTAR Scaled
Implicit Direct	Cor.	.45	-.39	-0.26	0.003	-0.33	-0.04	-0.07	0.10	-0.41
	Sig.	.85	.08	0.28	0.99	0.27	0.87	0.76	0.68	0.08
	N	21	21	20	18	13	18	19	19	19
Implicit Indirect	Cor.	-0.01	-0.22	-0.37	-0.02	0.07	0.10	0.31	0.42	0.22
	Sig.	0.99	0.34	0.11	0.95	0.83	0.69	0.22	0.09	0.40
	N	21	21	20	18	13	18	17	17	17
Explicit Direct	Cor.	0.09	0.14	-0.07	-0.32	-0.41	-0.21	0.47	0.27	0.27
	Sig.	0.68	0.56	0.77	0.20	0.17	0.40	0.05	0.28	0.28
	N	21	21	20	18	13	18	18	18	18
Explicit Indirect	Cor.	-0.20	0.29	-0.27	0.37	-0.16	0.04	0.32	0.004	0.27
	Sig.	0.40	0.22	0.26	0.13	0.60	0.89	0.19	0.99	0.27
	N	20	20	19	18	13	18	19	19	18

5.4.2.4 Comparison A: Implicit RT Analysis

Repeated measures ANOVA showed significant main effects for relatedness ($F(1, 53) = 8.78$, $p=0.01$), with faster RT to direct ($M=650 \pm 93$) than indirect pairs ($M=664 \pm 86$), reflecting successful priming. There was a two way interaction between relatedness and group ($F(2, 53) = 5.58$, $p=0.01$). There was a three way interaction between relatedness, pair type and group ($F(2, 53) = 6.64$, $p<0.01$).

Two one-way ANOVAs were used to explore the three way interaction. Priming was calculated to remove the effect of relatedness. There was a group difference on the direct task ($F(2, 55) = 6.57$, $p<0.01$), reflecting the fact that the schizophrenia group demonstrated less priming than either the control ($p<0.01$) or schiztypy group ($p=0.02$) (see Table 5.5).

5.4.2.5 Priming

T-tests were run to determine whether priming had occurred within each group. The control group demonstrated significant positive direct priming (t= -5.40, p>0.001) and negative priming in the indirect condition (t=2.34, p=0.03). This negative priming result was a surprise so the effect size was calculated to determine its importance. The Cohen's D effects size was only small (0.24). The schizotypy group demonstrated significant direct priming (t= -7.17, p>0.001) and no priming in the indirect condition (t=0.27, p=0.79). The schizophrenia group demonstrated no significant direct (t= -1.21, p=0.24) or indirect priming (t=0.83, p=0.42) (see Table 5.5 for priming and percentage priming scores).

Table 5.5 *Comparison A: Implicit Reaction Time Data*

Implicit	Participant Group	Relatedness	Mean in msec (SD)	Priming in msec (unrel-rel)	% Priming (1-rel/unrel) x100
Direct RT (250msec)	Controls (n=21)	Related	621.1 (81.2)	58.0 (49.2)**	8.2% (7.0)
		Unrelated	679.0 (96.8)		
	Schizotypy (n=18)	Related	628.1 (71.5)	52.7 (31.2)**	7.7% (4.5)
		Unrelated	680.8 (71.2)		
	Schizophrenia (n=19)	Related	680.9 (114.5)	12.4 (44.7)	2.0% (6.3)
		Unrelated	693.3 (98.3)		
Indirect RT (250msec)	Controls (n=21)	Related	660.9 (90.6)	-23.7 (46.4)*	-4.1% (7.6)
		Unrelated	637.2 (89.7)		
	Schizotypy (n=18)	Related	613.7 (71.8)	-3.2 (49.5)	-0.7% (8.2)
		Unrelated	610.5 (62.6)		
	Schizophrenia (n=19)	Related	708.7 (141.9)	-8.6 (43.0)	-1.1% (5.3)
		Unrelated	700.0 (125.7)		

* p>0.05, **p>0.001

5.4.2.6 Comparison A: Implicit Accuracy Analysis

Repeated measures ANOVA found no main effects or two way interactions. There was a three way interaction between pair type, relatedness and group ($F(2, 53) = 6.39$, $p<0.01$). Two one way ANOVAs were used to explore the three way interaction. Priming was calculated to remove the effect of relatedness. There was a group difference in priming for errors in the direct condition ($F(2, 55) = 9.54$, $p<0.001$) and no group differences for the indirect condition ($F(2, 53) = 0.62$, $p=0.54$). The group difference on the direct task was driven by the schizotypy group whose response pattern was characterised by a pattern of reduced accuracy in response to related compared to unrelated pairs. The opposite was true for the schizophrenia and healthy control groups both of whom demonstrated reduced accuracy in response to unrelated pairs compared to related pairs (see Table 5.6). The pattern of results demonstrated by the schizophrenia and control group is the one more typically reported in the literature.

Table 5.6 *Comparison A: Implicit Accuracy Data*

Implicit	Participant Group	Relatedness	Mean % (SD)	Priming (unrel- rel)
Direct Accuracy (250msec)	Controls (n=21)	Related	98.6 (1.7)	-2.4 (3.0)
		Unrelated	96.2 (3.5)	
	Schizotypy (n=18)	Related	96.9 (2.7)	2.2 (2.6)
		Unrelated	99.1 (1.5)	
	Schizophrenia (n=19)	Related	96.3 (4.8)	-2.6 (5.0)
		Unrelated	93.7 (6.6)	
Indirect Accuracy (250msec)	Controls (n=21)	Related	97.0 (2.8)	0.3 (4.2)
		Unrelated	97.3 (2.5)	
	Schizotypy (n=18)	Related	96.7 (3.6)	-1.1 (6.5)
		Unrelated	95.6 (7.5)	
	Schizophrenia (n=19)	Related	95.7 (5.5)	0.2 (4.3)
		Unrelated	95.6 (6.5)	

5.4.2.7 Comparison A: Explicit RT Analysis

Repeated measures ANOVA showed significant main effects for relatedness ($F(1, 53) = 59.52$, $p<0.001$), with faster RT to related (1253.5±181.3) than unrelated pairs (M=1432.7±239.4), reflecting successful priming. There was also a main effect for pair type ($F(1, 53) = 40.64$, $p<0.001$), with faster RT to direct (M=1219.4±219.1) than indirect stimuli (M=1478.1±273.3); and a main effect for group ($F(1, 53) = 3.46$, $p=0.04$), with fastest RT for controls (M= 1272.9 ± 145.1), followed by schizotypy (1334.9 ± 181.9), then schizophrenia (M= 1429.4 ± 220.7). There was a two way interaction between relatedness and group ($F(1, 53) = 3.37$, $p=0.04$).

ANOVAs were run to examine the two way interaction between group and relatedness. The first compared RT to related pairs and the second, to unrelated pairs. There were no group differences in RT to related pairs ($F(2, 53) = 1.46$, $p=0.24$), but there was a group difference in RT to unrelated pairs ($F(2, 53) = 4.71$, $p=0.01$). This difference stemmed from a slower RT to unrelated pairs in the schizophrenia group (M=1562.7 ± 306.4) compared to the control group (M=1345.7 ± 153.1, $p=0.02$). The schizotypy group (M=1399.3 ± 193.3) RT was not significantly different from schizophrenia ($p=0.08$) or controls ($p=0.75$) sitting between the two (see Table 5.7 for raw data and Figure 5.1).

5.4.2.8 Priming

Repeated measures t-tests were run to determine whether priming had occurred within each group. The controls demonstrated priming in both the direct ($t=-3.43$, $p>0.01$) and indirect conditions ($t=3.45$, $p>0.01$). The schizotypy group demonstrated significant priming in both the direct ($t=-3.49$,

p>0.01) and indirect conditions (t=-2.68, p=0.02). The schizophrenia group also demonstrated the same pattern of priming both the direct (t=-3.16, p=0.01) and the indirect condition (t=-4.58, p>0.001).

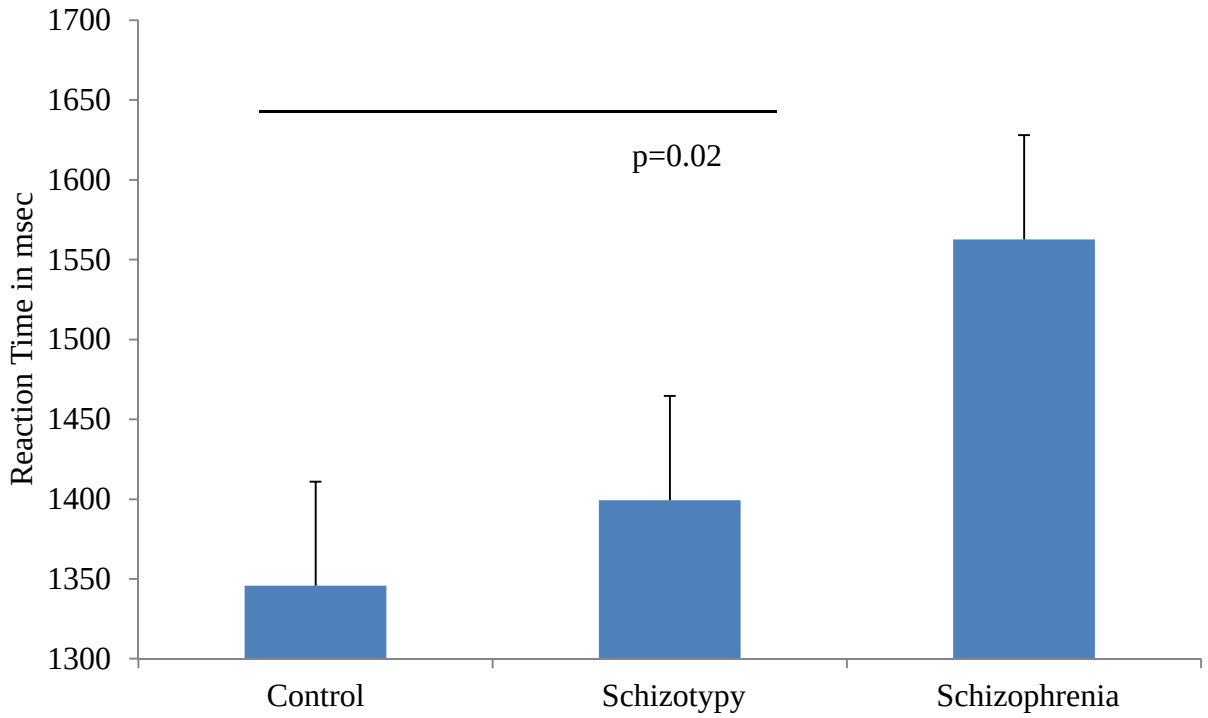

Figure 5.1 Comparison A: Comparison A: Reaction Time to Unrelated Pairs: Explicit Performance

Table 5.7 *Comparison A: Explicit Reaction Time Data*

Explicit	Participant Group	Relatedness	Mean (SD)	Priming (unrel- rel)	% Priming (1-rel/unrel) x100
Association Task RT (those who did 250)	Controls (n=20)	Related	1093.1 (130.8)	91.7 (207.4)**	9.4% (13.5)
		Unrelated	1199.3 (155.3)		
	Schizotypy (n=18)	Related	1115.9 (248.1)	132.1 (160.6)**	10.1% (12.6)
		Unrelated	1248.1 (233.1)		
	Schizophrenia (n=20)	Related	1237.8 (217.3)	214.2 (287.8)**	12.3% (16.2)
		Unrelated	1452.0 (350.5)		
Object Task RT (those who did 250)	Controls (n=20)	Related	1307.0 (315.3)	185.1 (239.7)**	11.8% (16.2)
		Unrelated	1492.1 (275.5)		
	Schizotypy (n=18)	Related	1424.9 (261.0)	125.6 (199.1)*	7.3% (11.9)
		Unrelated	1550.5 (292.6)		
	Schizophrenia (n=20)	Related	1354.3 (182.3)	342.3 (325.9)**	17.6% (14.2)
		Unrelated	1673.4 (357.6)		

* $p>0.05$, ** $p\geq0.01$

5.4.2.9 Comparison A: Explicit Accuracy Analysis

Repeated measures ANOVA showed that there was a significant effect for relatedness ($F(1, 53) = 7.0$, $p=0.01$), with reduced accuracy to related (M=90.1% ±7.9) compared to unrelated pairs (M=93.5% ± 8.7). There was a main effect of pair type ($F(1, 53) = 22.4$, $p<0.001$), with greater accuracy for direct (M=95.6% ± 4.2) than indirect pairs (M=87.8% ± 12.4); and finally there was a significant group effect ($F(1, 53) = 6.0$, $p<0.01$), with the schizophrenia group making the most errors

(M=87.8% ± 9.9), followed by schizotypy (M=92.4% ± 4.4) then controls (M=94.8% ± 2.2). There was a three way interaction between relatedness, pair type and group ($F(2, 53) = 6.5$, $p<0.01$).

Two one way ANOVAs were used to explore the three way interaction. Priming was calculated to remove the effect of relatedness. There was no group difference on the direct task ($F(2, 53) = 0.42$, $p=0.66$), but there was a group difference on the indirect task ($F(2, 53) = 4.49$, $p=0.02$). This group difference reflected a larger priming effect in the schizotypy group (M=14.6% ± 15.9) compared to the schizophrenia (M=1.6% ± 14.8, p=0.02) and control group (M= 4.1% ± 6.5, p=0.06) (albeit at trend level). An examination of the raw error data shows that this larger priming effect stems from a greater difficulty in correctly categorising related pairs as related (see Table 5.8).

Another two ANOVAs were run to examine how accuracy to related and unrelated pairs differed between the groups on the indirect task. The results showed that the groups differed in errors across both related ($F(2, 54) = 4.4$, $p=0.02$) and unrelated pairs ($F(2, 54) = 4.9$, $p=0.01$). The related result stemmed from the control group demonstrating greater accuracy than both the schizotypy (p=0.03) and the schizophrenia group (p=0.05) (see Figure 5.2). The unrelated result stemmed from the schizophrenia group demonstrating less accuracy than both the schizotypy (p=0.03) and the control group (p=0.02) (see Figure 5.3).

Table 5.8 *Comparison A: Explicit Accuracy Data*

Explicit	Participant Group	Relatedness	Mean (SD)	Priming (unrel- rel)
Association Task Accuracy (those who did 250)	Controls (n=20)	Related	95.6 (4.1)	0.9 (5.5)
		Unrelated	96.6 (3.2)	
	Schizotypy (n=18)	Related	97.9 (4.8)	-1.4 (9.5)
		Unrelated	96.5 (7.8)	
	Schizophrenia (n=41)	Related	92.7 (8.9)	1.4 (13.3)
		Unrelated	94.1 (7.3)	
Object Task Accuracy (those who did 250)	Controls (n=20)	Related	91.6 (5.5)	4.1 (6.5)
		Unrelated	95.6 (5.0)	
	Schizotypy (n=18)	Related	80.2 (12.4)	14.6 (15.9)
		Unrelated	94.8 (6.2)	
	Schizophrenia (n=40)	Related	81.9 (18.8)	1.6 (17.3)
		Unrelated	82.6 (23.6)	

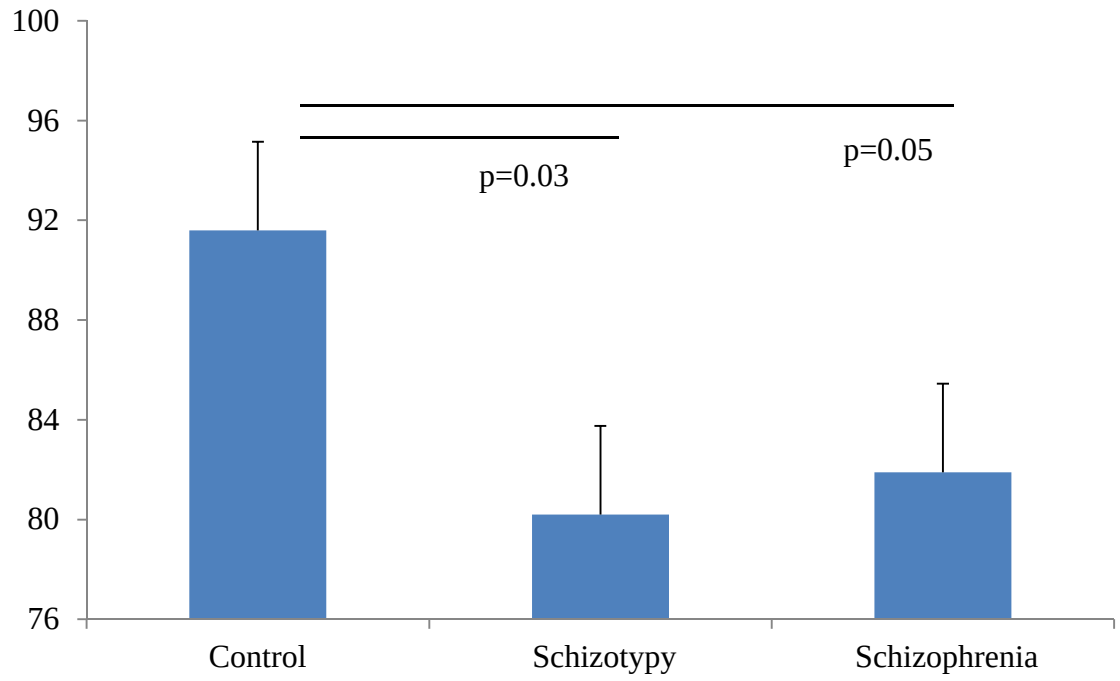

Figure 5.2 Comparison A: Reaction Time to Related Pairs on the Explicit Indirect Task

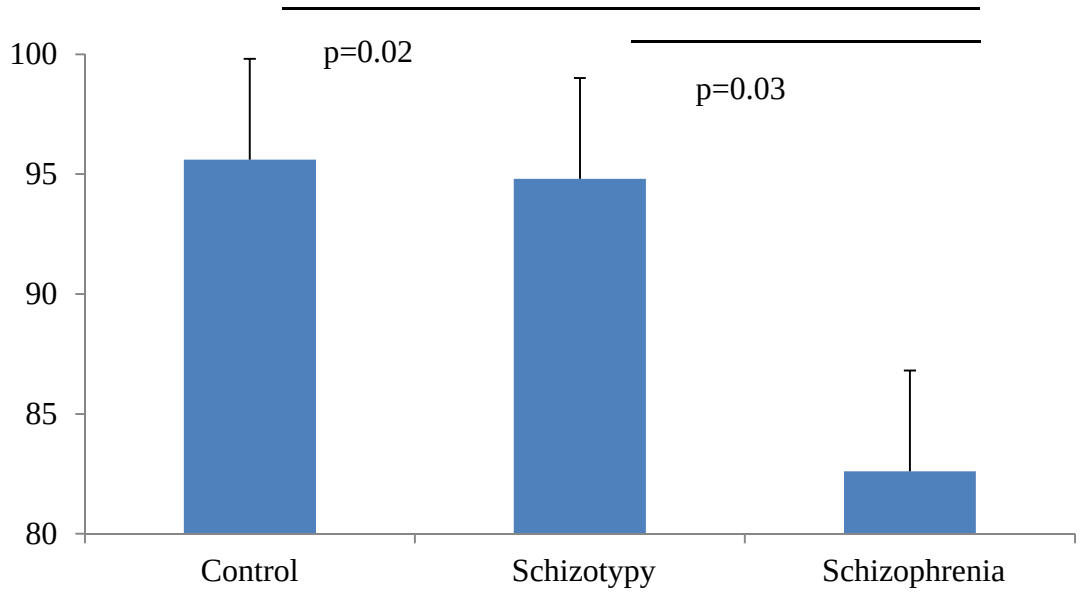

Figure 5.3 Comparison A: Reaction Time to Unrelated Pairs on the Explicit Indirect Task

5.4.3 Comparison B: Ketamine, schizophrenia, controls

5.4.3.1 Demographics

The three groups were compared on age and years of education. The WTAR data was not collected for the ketamine group as the design of the study was a repeated measures design so no WTAR data was necessary. There were significant differences between the three groups in age ($F(2, 58) = 11.88$, $p<0.001$), with the ketamine group ($M=25.82 \pm 4.29$) being significantly younger than both the schizophrenia ($M=40.50 \pm 9.51$, $p<0.001$) and the control groups ($M=36.32 \pm 14.53$, $p<0.01$). There was also a group difference between the three groups in years of education ($F(2, 58) = 3.98$, $p=0.02$), with the ketamine group ($M=18.5 \pm 2.84$) being more educated than the schizophrenia group ($M=15.63 \pm 4.1$, $p=0.02$). The control group ($M= 16.74 \pm 2.96$) was no different from the schizophrenia ($p=0.56$) or the ketamine group ($p=0.22$). There was no group difference between the schizophrenia ($M=97.20 \pm 15.55$) or control group ($M=104.56 \pm 10.62$) on WTAR scaled score ($F(2, 54) = 2.83$, $p=0.10$) (see Table 5.9). Correlational analysis demonstrated that there were no relationships between semantic performance and age or years education (see Table 5.4). As such, no covariates were entered into the following analyses.

Table 5.9 *Comparison B: Demographics*

450msec	Schizophrenia	Controls	Ketamine
Male/Female	13/7	11/8	7/15
Age (years)	40.50 (9.51)	36.32 (14.53)	25.82 (4.29)
Education (years)	15.62 (4.10)	16.74 (2.96)	18.50 (2.84)
WTAR IQ	97.20 (15.56)	104.56 (10.62)	
TLC (total)	3.80 (6.04)		
PANSS (Positive)	16.10 (4.97)		
PANSS (Negative)	12.20 (4.18)		
PANSS (General)	28.90 (8.66)		
PANSS (total)	57.20 (15.06)		
Length of illness	17.50 (9.24)		
CPZ mean dosage	511.75 (368.95)		

Table 5.10 *Comparison B: Correlations Between Demographics and Semantic Tasks*

% Priming 450msec		Controls			Schizophrenia			Ketamine	
		Age	Yrs. Educ	WTAR	Age	Yrs. Educ	WTAR	Age	Yrs. Educ
Implicit Direct	Cor.	0.22	-0.02	-0.28	0.08	0.22	0.27	-0.43	-0.42
	Sig.	**0.40**	**0.94**	**0.30**	**0.18**	**0.35**	**0.25**	**0.07**	**0.08**
	N	17	17	16	17	20	20	19	19
Implicit Indirect	Cor.	0.01	0.03	0.18	0.08	-0.29	-0.18	0.06	0.07
	Sig.	**0.96**	**0.92**	0.52	**0.75**	**0.26**	**0.50**	**0.82**	**0.78**
	N	17	17	16	20	17	17	19	19
Explicit Direct	Cor.	1.0	-0.34	**0.01**	-0.23	-0.13	-0.27	0.08	0.24
	Sig.	**0.70**	**0.16**	0.98	**0.34**	**0.58**	**0.25**	**0.74**	**0.34**
	N	18	18	17	20	20	20	18	18
Explicit Indirect	Cor.	0.03	-0.16	**0.05**	-0.19	-0.23	-0.30	0.03	0.04
	Sig.	**0.92**	**0.52**	0.85	**0.43**	**0.33**	**0.21**	**0.91**	**0.89**
	N	18	18	17	20	20	20	16	16

5.4.3.2 Slowed Processing Speed

There were significant group differences in overall RT to the implicit tasks ($F(2, 51) = 6.08$, $p<0.01$). This stemmed from the slower RT of the ketamine ($M=804.5 \pm 122.8$, $p<0.01$) and the schizophrenia group ($M= 770 \pm 156.3$, $p=0.03$) compared to controls ($M= 632.8 \pm 187.6$). The same

pattern of significant group differences existed for the explicit task ($F(2, 51) = 8.69$, $p<0.01$) with slower RT of both the ketamine ($M=1701.3 \pm 300.7$, $p<0.01$) and the schizophrenia group ($M=1580 \pm 307.1$, $p=0.02$) compared to controls ($M= 1322.5 \pm 195.7$). Due to the group differences on both implicit and explicit tasks, all follow up ANOVAs will be run using percentage priming.

5.4.3.3 Comparison B: Implicit RT Analysis

There was a main effect for pair type ($F(1, 51) = 15.21$, $p<0.001$), with a faster RT to directly ($M=718 \pm 171$) than indirectly related pairs ($M=755 \pm 176$). There was a main effect for relatedness ($F(1, 51) = 4.66$, $p=0.04$), with a faster RT to related ($M=731 \pm 169$) than unrelated pairs ($M=742 \pm 176$), reflecting successful priming; and finally, there was a main effect for group ($F(2, 51) = 6.08$, $p<0.01$), with the controls demonstrating the fastest RT ($M=633 \pm 188$), followed by schizophrenia ($M=770 \pm 156$), and finally the ketamine group ($M=805 \pm 123$). There was a two way interaction between group and pair type ($F(2, 51) = 3.94$, $p=0.03$). There were no three way interactions.

Paired samples t-tests were run to examine the two way interaction. Results showed that the controls ($M= -29 \pm 50$, $t= -2.47$, $p=0.02$) and the SZ group ($M= -75\pm 83$, $t= -3.73$, $p<0.01$) both demonstrated slower RT to the indirect task compared to the direct task. The ketamine group on the other hand, demonstrated no difference in RT between the two tasks ($M= -10 \pm 77$, $t= -0.54$, $p=0.60$) (see Table 5.11 for raw data).

5.4.3.4 Priming

T-tests were run to determine whether priming had occurred within each group. The control group demonstrated significant direct ($t=-2.54$, $p=0.02$) but no indirect priming ($t=0.76$, $p=0.46$). The

ketamine group demonstrated the same pattern with significant direct (t=-3.00, p=0.01) but no indirect priming (t=1.22, p=0.24). The schizophrenia group also demonstrated this pattern with significant direct (t=-2.35, p=0.03) and no indirect priming (t=0.80, p=0.44).

Table 5.11 *Comparison B: Implicit Reaction Time Data*

Implicit	Participant Group	Relatedness	Mean (SD)	Priming (unrel- rel)	% Priming (1-rel/unrel) x100
Direct RT (450msec)	Controls (n=18)	Related	603.6 (176.6)	29.2 (48.8)*	3.9% (6.5)
		Unrelated	632.8 (200.0)		
	Ketamine (n=19)	Related	781.1 (133.1)	36.5 (53.7)**	4.6% (5.9)
		Unrelated	818.3 (125.6)		
	Schizophrenia (n=20)	Related	715.6 (142.1)	29.1 (55.4)*	3.2% (7.3)
		Unrelated	744.7 (165.0)		
Indirect RT (450msec)	Controls (n=18)	Related	650.9 (193.9)	-4.0 (41.2)	-1.2% (5.7)
		Unrelated	643.9 (191.0)		
	Ketamine (n=19)	Related	818.6 (141.0)	-16.2 (66.1)	-2.4% (8.2)
		Unrelated	800.0 (128.9)		
	Schizophrenia (n=20)	Related	812.2 (157.4)	-9.0 (46.8)	-1.6% (6.0)
		Unrelated	803.1 (164.6)		

* $p>0.05$, ** $p\geq0.01$

5.4.3.5 Comparison B: Implicit Accuracy Analysis

There were no main effects or interactions when error data was analysed (see Table 5.12).

Table 5.12 *Comparison B: Implicit Accuracy Data*

Implicit	Participant Group	Relatedness	Mean (SD)	Priming (unrel- rel)
Direct Accuracy (450msec)	Controls (n=17)	Related	93.1 (24.1)	-0.7 (3.6)
		Unrelated	92.4 (24.0)	
	Ketamine (n=19)	Related	97.5 (2.9)	-1.2 (5.6)
		Unrelated	96.3 (5.1)	
	Schizophrenia (n=20)	Related	95.2 (6.6)	-0.3 (5.3)
		Unrelated	94.8 (6.0)	
Indirect Accuracy (450msec)	Controls (n=17)	Related	96.3 (2.7)	0.8 (3.1)
		Unrelated	97.1 (4.2)	
	Ketamine (n=19)	Related	98.3 (2.8)	-1.8 (4.2)
		Unrelated	96.5 (3.6)	
	Schizophrenia (n=20)	Related	95.7 (4.2)	1.4 (4.6)
		Unrelated	97.1 (3.9)	

5.4.3.6 Comparison B: Explicit RT Analysis

Repeated measures ANOVA showed significant main effects for relatedness ($F(1, 51) = 82.8$, $p<0.001$), with faster RT to related ($M=1420.2 \pm 286.9$) than unrelated pairs ($M=1640.0 \pm 358.3$), reflecting successful priming. There was an effect for pair type ($F(1, 51) =35.6$, $p<0.001$), with a faster RT to directly ($M=1446.3 \pm 360.0$) than indirectly related pairs ($M=1630.5 \pm 323.8$). Finally, there was a main effect for group ($F(1, 51) =8.7$, $p<0.01$), with controls demonstrating the fastest overall RT ($M=1322.5 \pm 195.7$), followed by schizophrenia ($M=1580.0 \pm 307.1$), and finally ketamine ($M=1701.3 \pm 300.7$). There was a two way interaction between relatedness and group ($F(1, 51) =6.7$, $p<0.01$). There was no three way interaction (see Table 5.13 for raw RT data).

Two one way ANOVAs were run to explore the two way interaction; the first examined related pairs. There was a group difference ($F(2, 51) = 6.22$, $p<0.01$) characterised by a slower RT from the ketamine group compared to controls. There was no difference between the schizophrenia and control group. With regards to unrelated RT performance there was a group difference ($F(2, 51) = 10.15$, $p>0.001$). Both the schizophrenia and ketamine group demonstrated slower RTs than the controls with no difference between the ketamine and schizophrenia group (see Figure 5.4 for the result pattern and Table 5.14 for significance).

T-tests were run to determine whether priming had occurred within each group. The controls demonstrated no significant priming on the Association task ($t=1.33$, $p=0.20$) but did on the Object task ($t=-2.48$, $p=0.02$). The ketamine group demonstrated priming to both the associative ($t=-4.11$, $p>0.001$) and the Object task ($t=-3.66$, $p>0.01$). The schizophrenia group also demonstrated significant priming on both the Associative ($t=-5.40$, $p>0.001$) and the Object task ($t=-7.14$, $p>0.001$).
Given that a specific hypothesis was made regarding normal priming on the Object task if the ketamine group were demonstrating an access deficit, priming was compared across the three groups. An independent t-test found that there was no significant difference in the percentage of priming achieved on the Object task between Ketamine ($M= 10.37\% \pm 12.54$) and controls ($M=11.70\% \pm 14.05$, $p=0.94$).

Table 5.13 *Comparison B: Explicit Reaction Time Data*

Explicit	Participant Group	Relatedness	Mean (SD)	Priming (unrel-rel)	% Priming (1-rel/unrel) x100
Association Task RT	Controls (n=20)	Related	1201.8 (244.7)	87.4 (249.4)	3.2% (13.2)
		Unrelated	1254.9 (258.3)		
	Ketamine (n=18)	Related	1461.3 (337.1)	268.8 (292.2)**	14.6% (11.9)
		Unrelated	1691.8 (396.3)		
	Schizophrenia (n=20)	Related	1396.5 (331.3)	194.0 (160.6)**	12.0% (8.9)
		Unrelated	1590.5 (378.1)		
Object Task RT	Controls (n=20)	Related	1336.3 (281.8)	160.8 (275.1)*	9.2% (16.3)
		Unrelated	1497.1 (318.8)		
	Ketamine (n=18)	Related	1712.1 (226.0)	214.5 (247.7)**	10.1% (12.6)
		Unrelated	1940.0 (355.4)		
	Schizophrenia (n=20)	Related	1449.6 (318.7)	433.6 (271.7)**	22.4% (12.9)
		Unrelated	1883.2 (350.7)		

* $p>0.05$, ** $p\geq 0.01$

Table 5.14 *Comparison B: Explicit Reaction Time Group Differences*

Task and Condition	Group	Comparison Group	Mean Difference	Significance
RT to related pairs	Control	Schizophrenia	-153.99	0.18
		Ketamine	-317.67	0.003
	Schizophrenia	Ketamine	-163.68	0.16
RT to unrelated pairs	Control	Schizophrenia	-360.85	0.002
		Ketamine	-439.88	0.001
	Schizophrenia	Ketamine	-79.02	0.73

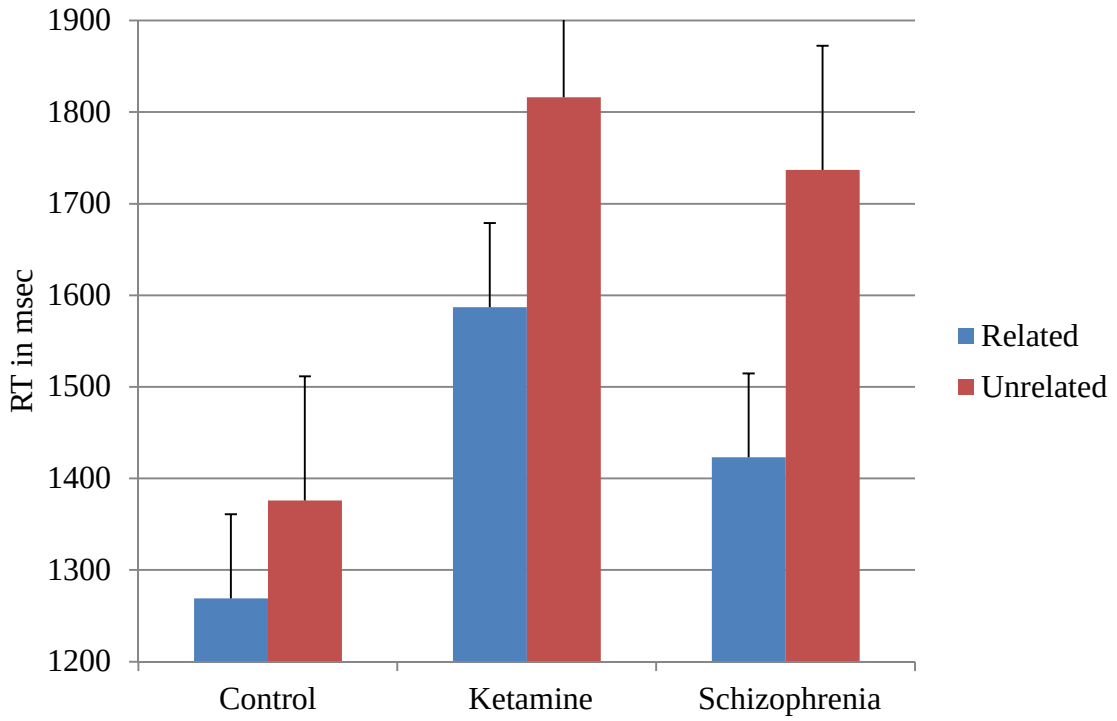

Figure 5.4 Comparison B: Reaction Time to Related and Unrelated Pairs on the Explicit Task

5.4.3.7 Comparison B: Explicit Error Analysis

Repeated measures ANOVA showed that there was a significant effect for relatedness ($F(1, 51) = 6.1$, $p=0.02$), with reduced accuracy to related (M=89.9% ± 7.6) compared to unrelated pairs (M= 92.7% ±7.9). There was a main effect of pair type ($F(1, 51) = 17.6$, $p<0.001$), with greater accuracy for direct (M= 93.0% ± 5.7) than indirect pairs (M= 88.7% ± 7.9). There were no group effects or two or three way interactions.

Table 5.15 *Comparison B: Explicit Accuracy Data*

Explicit	Participant Group	Relatedness	Mean (SD)	Priming (unrel- rel)
Association Task Accuracy (those who did 450)	Controls (n=20)	Related	95.1 (8.5)	0.3 (10.8)
		Unrelated	95.5 (4.7)	
	Ketamine (n=18)	Related	94.9 (5.2)	-5.2 (13.9)
		Unrelated	91.4 (11.6)	
	Schizophrenia (n=41)	Related	90.3 (8.9)	1.6 (12.0)
		Unrelated	91.9 (7.9)	
Object Task Accuracy (those who did 450)	Controls (n=38)	Related	87.2 (7.2)	7.6 (11.5)
		Unrelated	94.8 (8.9)	
	Ketamine (n=18)	Related	80.5 (13.2)	10.5 (18.9)
		Unrelated	91.0 (10.9)	
	Schizophrenia (n=40)	Related	85.9 (11.4)	5.9 (12.2)
		Unrelated	91.9 (10.7)	

5.5 Discussion

Two sets of analyses were performed to compare the schizotypy and ketamine analogue groups to schizophrenia. Comparison A was between the schizotypy, schizophrenia and controls, whilst comparison B was between the ketamine, schizophrenia and control groups. Given procedural differences, it was not possible to compare the two analogue groups directly to one another. All

participants performed the four semantic tasks that have already been presented in this thesis: implicit direct and indirect, and explicit direct and indirect. This discussion will begin with a statement about the failure of the implicit indirect task to produce significant priming. This will be followed by a review the findings generally, and in relation to previous chapters and then in relation to the four approaches suggested for each analogue.

5.5.1 Implicit Indirect Priming Task

Implicit indirect priming is a task, that has received a great deal of attention in schizophrenia research; with many authors reporting a hyperpriming effect in schizophrenia generally (Rossell & Stefanovic, 2007), or more specifically, among those schizophrenia participants with thought disorder (Pomarol-Clotet et al., 2008). An examination of the task in the current thesis has not revealed such clear findings. None of the groups examined showed implicit indirect priming at either a 250 or 450ms SOA (in fact at 250ms the healthy controls showed negative priming). Further, looking back to Chapter Two, in the placebo condition of the ketamine study, the RT data demonstrated that no significant implicit indirect priming had occurred there either. Among healthy controls specifically, it is not uncommon to find no significant indirect priming (Chui et al., 2003; Moritz et al., 2002; Sass et al., 2009; Spitzer, Braun, Hermle, & Maher, 1993). Chui's group found no indirect priming with a long SOA, Moritz's group found no indirect priming at a short SOA (specifically when using unrelated pairs as a baseline only), and Sass's group found non-significant negative priming at a short SOA. Breaking it down further, the Sass study included 15 associated pairs, 15 indirectly related pairs, 30 unrelated pairs and 30 non-words, an SOA of 350msec and an RP of 25%. For Moritz, the SOA was 200msec and the RP was 33.3%. Both studies combined directly and indirectly related pairs in the one task. The study by Chui did not provide details beyond the SOA of 950msec. The current study

included 30 direct, 30 indirect and 30 non-word pairs with a relatedness proportion of 50% using the Minzenberg calculation (2003). The relatedness proportion is somewhat higher than that used in other studies examining unconscious or implicit priming. It is therefore possible that controlled or post lexical processes played a role. Semantic matching is unlikely to be responsible as non-words constituted 50% of the task, and there were even numbers of related and unrelated pairs (30 of each per task). It is possible that some degree of expectation developed over the course of the task. This is a remote possibility however, as the indirect task was always presented first (and implicit tasks were always presented before explicit tasks), and due to the indirect nature of the pairs, it is less likely that the indirect relationships would be noticed when another task was provided as a distractor. Further, significant indirect priming was elicited at a long SOA (950msec) for the ketamine group (see Chapter Two). This suggests that it is not a matter of semantic matching or expectation as these would be more likely to play a role with a longer SOA. The most likely explanation comes from the nature of the indirect pairs themselves. To develop four word lists for the purpose of task balancing, a total of 120 indirectly related pairs needed to be created. To create so many indirect pairs required the inclusion of more distant indirect relationships (see Appendix C to examine the lists). The pairs used here may have been too subtle to be processed at a short SOA. As a result, it is likely that under these conditions, the pairs were treated as unrelated. It is difficult to compare the indirect pairs of the current thesis to previous studies because authors generally only report the relationship between prime and mediator, and mediator and target. This does not capture the relationship between prime and target. In the current thesis, associations between primes and their mediated targets were never above an association of ten. The association calculator is available at http://www.eat.rl.ac.uk/ and the methodology for their method of calculating association is outlined in the following paper (Kiss,

Armstrong, Milroy, & Piper, 1973). Due to the failure of this task at a short SOA to produce priming, it will be excluded from all further data interpretation in this chapter.

5.5.2 Comparison A: Implicit Tasks

Given that the indirect task has been excluded from interpretation, it is not possible to determine whether schizotypy is indeed associated with increased indirect priming at the implicit level. Results showed that on the direct task, the schizophrenia group demonstrated no significant RT priming whilst both the control and the schizotypy group did. This reduced priming is supported in the previous schizophrenia comparison paper on this task (see Chapter Four). The schizotypy finding on the other hand is not supported by the previous chapter (Chapter Three) which found schizotypy hyperpriming on the direct task. This may stem from the fact that the high schizotypy group were compared to a low schizotypy group in Chapter Three and it was determined that low schizotypy may not be a 'normal' comparison group unlike the controls included in this chapter. Error data showed that the schizotypy group made more errors to related than unrelated pairs whilst both the schizophrenia and control group showed the opposite pattern; greater errors in response to unrelated than related pairs.

An examination of the schizotypy cognitive literature was undertaken in an attempt to interpret this result. This investigation revealed that the schizotypy findings in this area are mixed (Barrantes-Vidal et al., 2003). Some authors find that only negative schizotypy is associated with cognitive problems (Dinn, Harris, Aycicegi, Greene, & Andover, 2002). Others suggest an association between high schizotypy generally and poor emotional intelligence (Aguirre, Sergi, & Levy, 2008), poor latent inhibition (Wuthrich & Bates, 2001), social functioning (Jahshan & Sergi, 2007) and across a range of cognitive skills (Hori et al., 2012). Still others report that verbal production is affected differently

depending on the presence of positive or negative schizotypy (Tsakanikos & Claridge, 2005). There is no literature, or indeed any theoretical reason as to why the schizotypy group should demonstrate more errors to related than unrelated direct pairs. The raw error data shows that the schizotypy and control groups' accuracy was at ceiling level. Therefore, this result most likely reflects this ceiling effect and not a schizotypy specific pattern of performance.

5.5.3 Comparison A: Explicit Tasks

Across the explicit tasks, a pattern emerged whereby the controls demonstrated the greatest speed and accuracy, followed by the schizotypy group, with the schizophrenia group demonstrating the slowest and least accurate performance.

5.5.4 Comparison A: The Four Approaches

Four approaches were taken to develop hypotheses about schizotypy performance. Given that the indirect task did not work and that there were no proposals made in relation to the direct tasks, the only performance to be examined is the explicit indirect task. The schizophrenia model, the access/storage debate and the implicit/explicit frameworks all suggested there would be abnormal performance on the indirect explicit task. It was proposed that any schizotypy deficits found would reflect milder versions of the deficits seen in schizophrenia. This is supported in so far that the schizotypy group demonstrated reduced accuracy to related pairs, similar to schizophrenia performance, but were more like controls in their accuracy to unrelated pairs. Therefore, the results for the hypothesis that the schizotypy group would demonstrate mild impairments on the indirect explicit task specifically were supported. This very nicely suggests a milder version of the semantic deficit seen in schizophrenia. Further, the findings from Chapter Three support this result with more indirect

errors generally associated with high schizotypy. The interpretation of this result must be general as more data would be needed to make specific conclusions about the exact nature of this response pattern. It may be that the semantic store or access to the store is impaired enough that ambiguous/indirect relationships are difficult to retrieve whilst the more well maintained direct relationships remain intact.

5.5.5 Comparison B: Implicit Tasks

The 450ms SOA examination of schizophrenia and ketamine are novel to this chapter so the schizophrenia data will be interpreted in comparison to the control group first, then the ketamine group will be compared to both the schizophrenia and control results.

5.5.6 Implicit Priming in Schizophrenia

Given the failure of the indirect implicit task to elicit priming in any group, hypotheses relating to this task cannot be addressed. The direct results for the implicit task are therefore examined. The only difference between schizophrenia and controls performance was that the schizophrenia group were slower overall. The schizophrenia results were therefore unremarkable for the implicit tasks.

5.5.7 Implicit Priming Results: Comparison between Schizophrenia, Ketamine and Controls

Overall, on the implicit tasks, there was a stepwise slowing in RT starting with the controls who were the fastest, followed by schizophrenia, followed by ketamine. While the schizophrenia and control group were slower on the indirect compared to the direct task, the ketamine group demonstrated no difference in overall RT to either task. Given that the groups showed no differences in errors or in degree of priming, it suggests that the ketamine group were able to process the pair relationships in a

similar way to the schizophrenia and control group. Given the extreme slowing in overall RT of the ketamine group, the finding of no difference in RT between the direct and indirectly related pairs is probably a result of the intoxication effect and not a semantic specific deficit.

5.5.8 Comparison B: Explicit Tasks

There was a group effect in RT in the same order seen on the implicit tasks. Controls were faster than the schizophrenia group who were faster than the ketamine group. The control group demonstrated non-significant priming (3.2%) on the direct explicit task. This might seem unusual, but after looking at the speed of the RT's recorded to both related and unrelated pairs; it is likely that the task was too easy leading to a ceiling effect. The ketamine groups performance was characterised by a general slowing in RT. This same slowing was evident on the implicit tasks.

The schizophrenia group, on the other hand, demonstrated a specific slowing in response to unrelated pairs on both explicit tasks. Other than a general slowing effect, this is the only schizophrenia group difference found.

5.5.9 Comparison B: The Four Approaches

Once again, given that the indirect implicit task did not work and given that no hypotheses were made with regards to the direct tasks, the four approaches can only be examined in terms of the explicit indirect task. There was no ketamine data on this task so it is the schizophrenia, access/store and implicit/explicit approaches that are examined. Both the schizophrenia model and the implicit/explicit model predict that performance on this task should be abnormal. With regards to the access/store framework, it was hypothesised that there would be no effect of ketamine on the explicit tasks as the

instruction provided should have ameliorated any access difficulties elicited by the drug. The results support this hypothesis as there was no difference in percentage priming between the ketamine and control group. This result therefore supports the proposition that ketamine impairs semantic access.

5.5.10 Schizophrenia: Performance across tasks and SOAs

The schizophrenia group demonstrated generally slower RT and more errors than the control group across the implicit tasks at both the 250msec and 450msec conditions and across the explicit tasks. The two schizophrenia groups were matched on major demographic variables associated with variation in priming performance (age, premorbid verbal intelligence, total years of education, Chlorpromazine equivalents) and as such, the priming results across the 250msec and 450msec SOAs will be treated as a general schizophrenia finding. Schizophrenia was associated with no significant direct priming at 250msec but intact direct priming at 450msec. In their review, Minzenberg and colleagues (2002) reiterated the proposal of earlier researchers (Ober et al., 1997) that schizophrenia can be associated with a delay in the onset in the spreading of activation. The current results do fit with this idea given the success of priming at 450msec.

The finding of normal RT to related and slowed RT to unrelated pairs across the explicit tasks was demonstrated across both the 250msec and 450msec schizophrenia samples. This suggests that when semantic pairs are examined explicitly, a schizophrenia group will benefit from being directed towards the semantic relationship. This direction does not compensate for a difficulty in recognising unrelated information. The structure of semantic memory in this group of schizophrenia participants appears to be grossly intact. They were able to prime to both direct and indirect pairs explicitly. This suggests that even indirect relations are reasonably accessible/intact. The exact reason for the slowing

in response to unrelated pairs is not clear. Given the reasonably intact store, it may be that there is excessive spreading in the semantic system which is compensated for with extra time.

5.6 Conclusions

The schizotypy results provide evidence that this is a useful analogue to schizophrenia performance as this group demonstrated a milder but similar pattern of performance to the schizophrenia group. The ketamine results suggest that this is may be a good model for access deficits but does not provide a general model for schizophrenia semantic dysfunction because it does not impair semantic storage. There is some evidence that chronic ketamine abuse may lead to changes in the semantic store (Morgan & Curran, 2006) and as such, future studies may be able to rely on participants with this pattern of ketamine use to examine store like deficits in an analogue group.

CHAPTER 6. CATEGORY FLUENCY IN SCHIZOPHRENIA RESEARCH: IS IT AN EXECUTIVE OR SEMANTIC MEASURE?

DECLARATION FOR THESIS CHAPTER 6

Declaration by candidate:

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, data collection, data analysis and writing of manuscript.	90%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Susan Rossell	Supervisor of Erica Neill's PhD. Provided assistance in data analysis and proof reading of the manuscript

Candidates Signature: [redacted] **Date: 14/01/13**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from 2009

Susan Rossell Signature: [redacted] **Date: 14/01/13**

6.1 Chapter Guide

This is the first of three chapters concerned with examining the relationship between executive functioning and other areas of cognition. This chapter consists of an article that is under review with Cognitive Neuropsychiatry. There is no additional information included in this chapter beyond the submitted article as section 1.2 in Chapter One contains additional information regarding semantic and executive function in schizophrenia.

6.2 Abstract

Categorical fluency is the main measure of semantic function in schizophrenia (SZ). Two meta-analyses have supported the tasks' efficacy in measuring semantic function (Bokat and Goldberg, 2003; Henry and Crawford, 2005); a more recent meta-analysis, which included additional experiments, suggested that executive function is the predominant determinant of semantic fluency performance in SZ (Doughty & Done, 2009). This study employed a novel approach to examine this latter position by using a fluency task that incorporates both semantic and executive elements (animals by size). Forty two SZ participants and forty healthy controls performed three fluency tasks: executive (F, A, S), semantic (Body Parts) and semantic/executive. Executive fluency output was not significantly different between groups or only mildly impaired depending on method of executive fluency calculation. Semantic fluency was impaired in SZ, and executive/semantic performance in SZ was impaired to a similar degree to semantic performance. Group differences on the semantic/executive task remained when executive function was controlled for and disappeared when semantic fluency effects were controlled for. The addition of the novel semantic/executive task clarified the role of semantic memory function in fluency performance. The findings support earlier meta-analyses (Bokat & Goldberg, 2003; Henry & Crawford, 2005) in their conclusion that the semantic fluency task is an accurate measure of semantic memory function in SZ.

6.3 Introduction

6.3.1 Fluency in Schizophrenia

Schizophrenia (SZ) is associated with significant deficits in semantic memory (Chen, Wilkins, & McKenna, 1994; McKenna, Mortimer, & Hodges, 1994; Rossell et al., 2008; Rossell & David, 2006). Semantic memory describes our memory for factual information for example, the names of capital cities or the knowledge that bananas are fruit; it is our 'general knowledge' store (Tulving, 1972). Evidence suggests that this system is hierarchically organized with concepts falling under category headings like 'animals' or 'vegetables' (Caramazza & Mahon, 2003; Tyler & Moss, 2001). The semantic fluency task requires participants to generate as many words as they can belonging to such a category so it requires access to the semantic memory store. The semantic fluency task correlates with other recognized measures of semantic memory including naming, sorting and definition generation (Bozeat, Lambon Ralph, et al., 2000; Hodges et al., 1992; Vinogradov et al., 2003) providing convergent validity for the task. Given the contributions of semantic memory to this task, poor semantic fluency performance is used as evidence for a semantic deficit in SZ. Compared to healthy controls, SZ group's poor semantic fluency performance has been characterized by reduced overall output, reduced numbers of examples from sub-categories ('farm animals' for example), reduced switching between sub-categories and higher error rates (McKay et al., 1996; Robert et al., 1998; Sumiyoshi, Ertugrul, Yagcioglu, & Sumiyoshi, 2009).

The semantic fluency task does not tap semantic memory exclusively. Skills including attention and processing speed also contribute to performance (Goldberg et al., 1998). One way to isolate the semantic component of the task is to compare it to a fluency task with similar dependence on the more basic cognitive skills but without the semantic element. A task often used for comparison is a

phonemic fluency task which requires participants to generate all the words they can beginning with a specific letter. In healthy controls, more overall output is produced on the semantic than the phonemic fluency task. This is thought to reflect the fact that the phonemic task is more difficult with a greater reliance on executive functions (Spreen & Strauss, 2008) (NB, in this paper, from this point, 'phonemic fluency' will be described as the 'executive fluency' task to reflect the proposed underlying processes associated with the task). Executive functions describe a range of higher level thinking skills. These include, but are not limited to, complex attention, abstract thought, planning/organizing, inhibition and self-monitoring (Baddeley & Hitch, 1974; Delis et al., 2001; Lezak et al., 2004; Luria, 1966; Norman & Shallice, 1986; Stuss & Alexander, 2000).

In those disorders associated with semantic deficits, such as Alzheimer's or semantic dementia (Henry, Crawford, & Phillips, 2004), the healthy pattern of performance of greater semantic than executive fluency output is reversed with reduced output for semantic compared to executive fluency. Two meta-analyses examining SZ performance on both semantic and executive fluency (Bokat & Goldberg, 2003; Henry & Crawford, 2005) have found that semantic fluency performance was more impaired than executive fluency performance, a pattern similar to that seen in dementia. This led the authors to conclude that (1) semantic memory is impaired in SZ, and (2) the semantic fluency task is appropriate for detecting this deficit.

A more recent meta-analysis found the opposite pattern of results: greater executive than semantic impairment in SZ (Doughty & Done, 2009); the same pattern that is observed in healthy controls. However, SZ participants produced significantly less output on both fluency tasks compared to healthy controls. Doughty and Done (2009) reported that the discrepancy between the findings of

their meta-analysis and the two previous meta-analyses may be the result of their inclusion of additional papers not available at the time of the earlier reviews, and their differing search and inclusion criteria. They concluded that when the semantic fluency task is used in SZ, it may not be tapping into semantic memory. Instead, reduced output in SZ may reflect a more general deficit that is likely executive in nature.

The possibility that semantic fluency is dictated more by executive than semantic skills has been raised previously (Barrera et al., 2005; Holthausen et al., 2003; Kiefer, Ahlegian, & Spitzer, 2005; Stirling et al., 2006). It has been suggested that performance on the semantic fluency task requires the executive skills of task maintenance, working memory, monitoring and inhibition (Lezak et al., 2004).

Alternatively, there are those who suggest that semantic fluency is little affected by executive skills as the hierarchical organization of semantic memory accommodates the recall of related information, thus accessing different 'Animals' or 'Body Parts' requires little active retrieval, and is therefore automatic in nature (Giovannetti, Goldstein, Schullery, Barr, & Bilder, 2003). Finally, while frontal lesions can impair both tasks, there is evidence that temporal lesions (suggested to be the home of semantic memory) impair semantic fluency specifically (Henry & Crawford, 2004).

6.3.2 A new approach

Traditional fluency studies compare executive fluency (in this study the traditional letters of F, A and S) and semantic fluency (in this study 'Body Parts'). A new approach is needed to clarify the executive influences on the semantic fluency task within the SZ population. Instead of trying to reduce the executive elements however, it may be that increasing them to a more recognizable/measurable

level will clarify the issue. To examine the contribution of executive function to the semantic fluency task, in addition to the traditional executive and semantic fluency options, a semantic/executive fluency task was included. This task requires participants to list animals from smallest to largest over a 60 second period. This version adds the executive elements of reasoning, judgment, organization and planning to the traditional semantic task (Chlipala, 2010). This task has not been well published as it is an experimental measure, but has been used in Australia by Tucker and colleagues at Victoria University (Chlipala, 2010). Unpublished thesis data demonstrated that this task is more sensitive in detecting executive deficits in ADHD children than Trails B (Roper, 2007) and was also able to detect executive problems in inhalant abusers not detected by Trails B or a Stroop task (Baliz, 2008). This suggests it is capable of tapping into even subtle executive problems. There is also evidence, based on 124 healthy controls, of face validity with animals by size correlating significantly with Trails B ($r = -0.59$, $p<0.001$). There is very little normative data for the task but Ewing reports, in an unpublished dissertation, norms for 11 healthy participants for animals by size over a minute is $M=15 \pm 2$ (Ewing, 1985). In addition, Chlipala's (2010) thesis contained norms by age group. When these were collapsed across the age groups relevant to this study (18-65) the average output for 76 participants was as follows: $M=14.48 \pm 3.4$.

6.3.3 Executive and Semantic Fluency Measures

The semantic fluency task in this study employed the category 'Body Parts'. The body parts version of semantic fluency was used because it provides a similar level of output to the more traditionally used category of 'Animals' and because there are guidelines on matching this task to the traditional executive fluency task (F,A and S) on discriminant validity (Melinder, Barch, Heydebrand, & Csernansky, 2005). The category of 'Animals' was not used due to the possibly confounding effects

of using ‘Animals’ in addition to the new task ‘Animals by size’. Beatty (2002) included control data from 87 participants and found that the average results for animals was 20.9 (s.d.=5.4) and for body parts 26.9 (6.5), and Moreno-Martinez et al. (2008) reported output for 72 healthy controls for animals was 22.24 (6.14) and body parts 25.93 (5.13).

For the executive fluency task, the traditional letters of F, A and S were used as there was no confounding factor that required an alternative be sought. There are no agreed upon methods for comparing executive and semantic fluency and often, no justification for the choices authors have made is offered. Some authors include additional semantic categories and compare the means for three executive to three semantic categories (Granholm, Chock, & Morris, 1998; Kosmidis et al., 2005; Kozora & Cullum, 1995; Salmon, Heindel, & Lange, 1999), others have compared the average of FAS (Joyce et al., 1996; Kremen, Seidman, Faraone, & Tsuang, 2003) and still others have used one letter and one semantic category (Grogan, Green, Ali, Crinion, & Price, 2009; Murphy, Rich, & Troyer, 2006; N'Kaoua, Lespinet, Barsse, Rougier, & Claverie, 2001).

For the current study, two different methods of comparison were used (1) a version that matched the amount of raw output on the executive to the semantic task (Melinder et al., 2005), and (2) a version that matched the raw output on the executive to the new semantic/executive task. With regards to method (1) Melinder et al. (2005) in their paper on discriminant validity of fluency tasks, specifically devised a way to match executive and semantic fluency on discriminant validity in a healthy control and SZ sample. They determined that when using the category of body parts it was best to compare the results to the summed output from the letters ‘A’ and ‘S’ from the executive fluency task to maintain good discriminant validity. For method (2) research suggests that both ‘S’ (M=15±

4.7) and ‘F’ (M=14.4 ± 4.5) have a similar level of output and both are associated with higher output than the letter ‘A’ (M=11.9 ± 4.4) (Tombaugh, Kozak, & Rees, 1999). It was determined that the average of ‘F’ and ‘S’ would be the most similar to the output for the semantic/executive task (M=15 ± 2) (Ewing, 1985); (M=14.48 ± 3.4) (Chlipala, 2010). This method of matching tasks on total output ensures a similar level of difficulty.

If semantic fluency is indeed disproportionately impaired in SZ as the majority of research to date suggests, then the SZ group will (1a) demonstrate worse semantic performance than controls, and (1b) will demonstrated normal or less seriously impaired performance on the executive task (measured as a smaller effect size difference between groups on the executive versus semantic fluency task). Based on the above assumption, it is also hypothesized that the SZ group will (2) demonstrate worse semantic/executive performance than controls (due to the semantic elements of the task); and finally (3) will be more impaired on the semantic/executive task than the phonemic task (for the same reason). It is expected that both methods of fluency matching will support these hypotheses.

It is also possible that the semantic/executive task will create a greater burden on executive functions than does the executive fluency task. Ordering animals by size may require more working memory and, almost certainly, more organization than generating words beginning with a specific letter. It would therefore be possible for the hypotheses relating to this task (hypotheses 2 and 3) to be supported (worse semantic/executive than executive performance) without necessarily implicating a semantic memory deficit. If these hypotheses are supported, ANCOVA’s controlling for the semantic influence on the task will be run to determine the driving force behind poor semantic/executive performance. If group differences remain significant, then it must be conceded that executive

influences may be responsible for results. If group differences are no longer significant then semantic memory is likely responsible for reduced output.

Finally, fluency performance has been linked to a number of psychotic symptoms. Positive thought disorder (Kuperberg, McGuire, & Anthony, 1998; McKenna et al., 1994; Rossell et al., 1999), delusions/paranoia (Goldberg et al., 1998; Spitzer, 1997) and negative symptoms (Joyce et al., 1996) have all been associated with reduced semantic output. It is therefore hypothesized that thought disorder, delusions and negative symptoms will be associated with reduced semantic output.

6.4 Methods

6.4.1 Participants

Forty two SZ participants were recruited from the Alfred Hospital and surrounding community mental health services. Diagnosis was confirmed using the Structured Clinical Interview Diagnostic (SCID) (First et al., 1997) and current symptoms were evaluated with the Positive and Negative Symptoms Schedule (PANSS) (Kay et al., 1987). Four global scores were calculated from the PANSS interview: Positive (maximum score 49) which includes hallucinations, delusions and conceptual disorganization; Negative (maximum score 49) which includes measures of alogia and blunted affect. General (maximum score 112) collecting information about unusual thoughts, anxiety, depression and guilt. Finally, a total score can be calculated with a maximum of 210. All patients needed to score >40 but <80 on the total PANSS score to be accepted into the study (Leucht et al., 2005). This ensured all patients were mild to moderately unwell at the time of testing, but not severe, to ensure that they were able to provide consent and understand all study instructions. The negative global scale and a single item measuring delusions were included in analysis based on reports from previous research (Goldberg

et al., 1998; Joyce et al., 1996; Spitzer, 1997). Thought disorder was additionally rated throughout the SCID using the Thought Language and Communication scale (TLC) (Andreasen, 1979). Forty healthy controls were recruited from advertisements around the Alfred Hospital and Monash University. They were screened for psychiatric illness using the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962). Participants for both groups were excluded if they had any verbal learning/reading disorders, any history of drug abuse/addiction, ECT in the past six months, any history of significant head injury (loss of consciousness more than five minutes or hospitalization required), overdose or neurological disorders. Controls were excluded if they reported any psychiatric disorder and SZ participants were excluded if they had a comorbid psychiatric diagnoses (see Table 1. for demographic information).

6.4.2 Fluency Tasks

The executive tasks requested participants name as many words as they could beginning with the letters F, A and S; the semantic task requested as many body parts as possible and the semantic/executive fluency task requested that participants name as many animals as possible, avoiding repetitions and ever increasing in size (whether by height or weight). All three fluency tasks collected responses for 60 seconds. Raw scores (total number of correct responses) was analyzed. Errors were removed from the total score, and were additionally analyzed.

6.4.3 Data Analysis

Past literature suggests that fluency performance is significantly affected by education and verbal IQ (Spreen & Strauss, 2008). Pearsons Product Moment Correlations were run between fluency performance on the three versions (including both words generated and errors) and WTAR score (the measure of verbal IQ), education and age (because the groups differ in age) to determine whether this relationship existed in our sample. Two by three way repeated-measures ANOVA's were conducted to investigate total output and error rates across the three fluency tasks comparing SZ to controls. As education did show a positive correlation, education was entered into as a covariate in these analyses. Post-hoc ANOVA and ANCOVA were run if (1) there were significant interactions and/or (2) if they were necessary to address specific hypotheses.

In the SZ group only, CPZ equivalents and length of illness were correlated to determine their influence on fluency performance. Further to examine the relationship between fluency (including both output and errors) and symptoms of psychosis, correlations were run with PANSS negative, a single delusion item from the PANSS and the thought disorder scale. Significance levels of all correlations were adjusted to take into account the multiple variables and a conservative alpha of 0.01 was used. For hypothesis (1b), comparing group differences on degrees of impairment on two fluency tasks, Cohen's d calculation of effect size will be used.

6.4.4 Analysis to be run if semantic/executive fluency is more impaired in SZ

ANCOVAs will be run controlling for executive fluency to determine whether performance on the semantic/executive task was driven by the same skills as those required in the executive fluency task (one ANCOVA will be run using method (1) of executive fluency analysis and another using

method (2)). If group differences remain after controlling for executive fluency, a further ANCOVA will be run controlling for the influence of semantic fluency. If group differences disappear, reduced SZ performance can be attributed to a semantic deficit, if they remain, performance may be due to different executive skills than those required by the executive fluency task.

6.5 Results

T-tests showed that there were significant group differences in age ($t= -3.05$, $p<0.01$) (see Table 6.1). Using a conservative p value of 0.01, there was a trend towards a significant correlation between total years of education and method (1) for calculating executive fluency ($r= 0.26$, $n=81$, $p=0.02$). There were significant correlations between total years of education and method (2) ($r=0.35$, $n=81$, $p=0.001$) and semantic fluency ($r= 0.30$, $n=81$, $p=0.01$). Total years of education was thus used as a covariate in the analyses (Miller & Chapman, 2001). Age did not show any relationship with any of the fluency measures.

Table 6.1 *Demographic Information for Schizophrenia and Controls*

	Schizophrenia	Controls
Male/Female	25/17	19/21
Age (years)	41.05 (10.76)*	31.60 (11.80)
Education (years)	15.14 (4.01)	16.20 (2.56)
WTAR IQ	99.81 (14.35)	103.21 (9.25)
TLC (total)	2.60 (5.41)	0.51 (2.15)
PANSS (Positive)	15.52 (4.52)	
PANSS (Negative)	11.43 (3.42)	
PANSS (General)	28.29 (8.84)	
PANSS (total)	55.24 (14.22)	
Length of illness	18.08 (10.28)	
CPZ mean dosage	485.22 (348.11)	

** $p<0.05$ using one way ANOVA across groups*

6.5.1 Method (1) (A + S)

A 3x2 way repeated-measures ANCOVA, with education as a covariate, was run to examine total output on the 3 fluency tasks using method (1). There was a main effect for fluency (F (2, 77) = 3.45, p=0.03), a main effect for group (F (1, 78) = 11.82, p=0.001, *d*=0.75) and a main effect for years of education (F (2, 78) = 6.27, p=0.01)[2]. The fluency effect was characterised by greatest output for semantic (M= 29.03 ± 7.34), followed by executive (M=29.35 ± 8.82) then the semantic/executive fluency (M= 29.33 ±8.81). The group effect was characterised by greater output for controls (M= 26.50 ± 5.32) than SZ (M=22.4 ± 5.63) (see Figure 6.1 for all fluency output). There was a two-way interaction that approached significance between group and fluency (F (2, 77) = 2.84, p= 0.06). Due to the specific nature of our hypothesis, a one way ANOVA was performed to explore the exact nature of this interaction despite the fact that it was only at trend level. There was no significant group difference on the executive task (F (1, 79) = 2.98, p=0.09) with the SZ group attaining 90% of healthy control performance. There was a significant difference on the semantic/ executive task (F (1, 79) = 10.65, p<0.01, *d*= 0.73), with the SZ group attaining 76% of healthy control performance. Finally, there was a significant group difference for the semantic only version (F (1, 79) =21.85, p<0.001, *d* = 1.04), with 81% of healthy control performance attained (see Table 6.2).

[2] The ANCOVAs were re-run with only patients on atypical medications (i.e. removing 5 participants) for both methods and there were no changes in results.

Table 6.2 *Fluency Output*

Fluency Task	Group (N)	Raw Output Mean (SD)	
Semantic	Schizophrenia (41)	25.63 (7.12)	p<0.001
	Controls (40)	32.43 (5.89)	
Semantic/Exec	Schizophrenia (41)	13.24 (4.28)	p<0.01
	Controls (40)	16.70 (5.21)	
Executive (A+S)	Schizophrenia (41)	27.68 (8.25)	p=0.09
	Controls (40)	31.03 (8.25)	
Executive (F+S)/2	Schizophrenia (41)	14.71 (4.79)	p=0.04
	Controls (40)	16.90 (4.61)	

An ANCOVA was conducted to determine whether group differences on the semantic/executive task and the semantic task remained after controlling for the contribution of executive fluency as calculated using method 1. Group differences remained on both the semantic/executive ($F(1, 78) = 7.77$, $p=0.01$) and the semantic fluency task ($F(1, 78) = 6.71$, $p=0.01$). A 3x2 way repeated-measures ANOVA was conducted to investigate errors using method (1). There were no significant correlations between demographic variables and error performance so no covariates were included in the analysis. The results showed no main effect for fluency ($F(2, 75) = 2.27$, $p= 0.11$) or group ($F(1, 76) = 2.88$, $p = 0.09$). As such, further analysis of error data was not conducted.

6.5.2 Method (2) (F + S)/2

A 3x2 way repeated-measures ANCOVA, with education as a covariate, was run to examine total output on the 3 fluency tasks using method (2). There was a main effect for fluency ($F(2, 78) = 9.76$, $p<0.001$) and a main effect for group ($F(2, 78) = 15.77$, $p<0.001$). There was no main effect for education ($F(1, 78) = 0.11, 0.74$). There was also a significant interaction between group and fluency ($F(2, 78) = 7.28$, $p=0.001$). The order of output remained unchanged using method 2: Semantic > executive> semantic/executive. The group effect was also unchanged with greater output for controls ($M= 22.01 \pm 4.32$) than SZ ($M= 17.86 \pm 4.47$) ($F(1, 78) = 15.77$, $p<0.001$, $d = 0.94$). A one way ANOVA was performed to determine the role of executive fluency (calculated using method 2) in the fluency by group interaction. The group difference on the executive task ($F(1, 79) = 4.47$, $p=0.04$, $d= 0.47$), remained using method (2) with the SZ group attaining 88% of healthy control performance. An ANCOVA was conducted to determine whether group differences on the semantic/executive task and the semantic task remained after controlling for the contribution of executive fluency as calculated using method 2. Group differences remained on both the semantic/executive ($F(1, 78) =5.99$, $p=0.02$) and the semantic fluency task ($F(1, 78) = 16.33$, $p<0.001$).

A 3x2 way repeated-measures ANOVA was conducted to investigate errors using method (2). There were no significant correlations between demographic variables and error performance so no covariates were included in the analysis. The results showed no main effect for fluency ($F(2, 75) = 2.63$, $p= 0.08$) or for group ($F(1, 76) = 4.06$, $p = 0.05$). As such, further analysis of error data was not conducted.

6.5.3 Semantic Fluency vs. Semantic Executive Fluency

An ANCOVA was run to examine whether group differences remained on the semantic/executive performance when semantic influences were controlled for. When semantic fluency was included as a covariate, group difference on the semantic/executive task were not significant (F (1, 78) = 0.82, p=0.37).

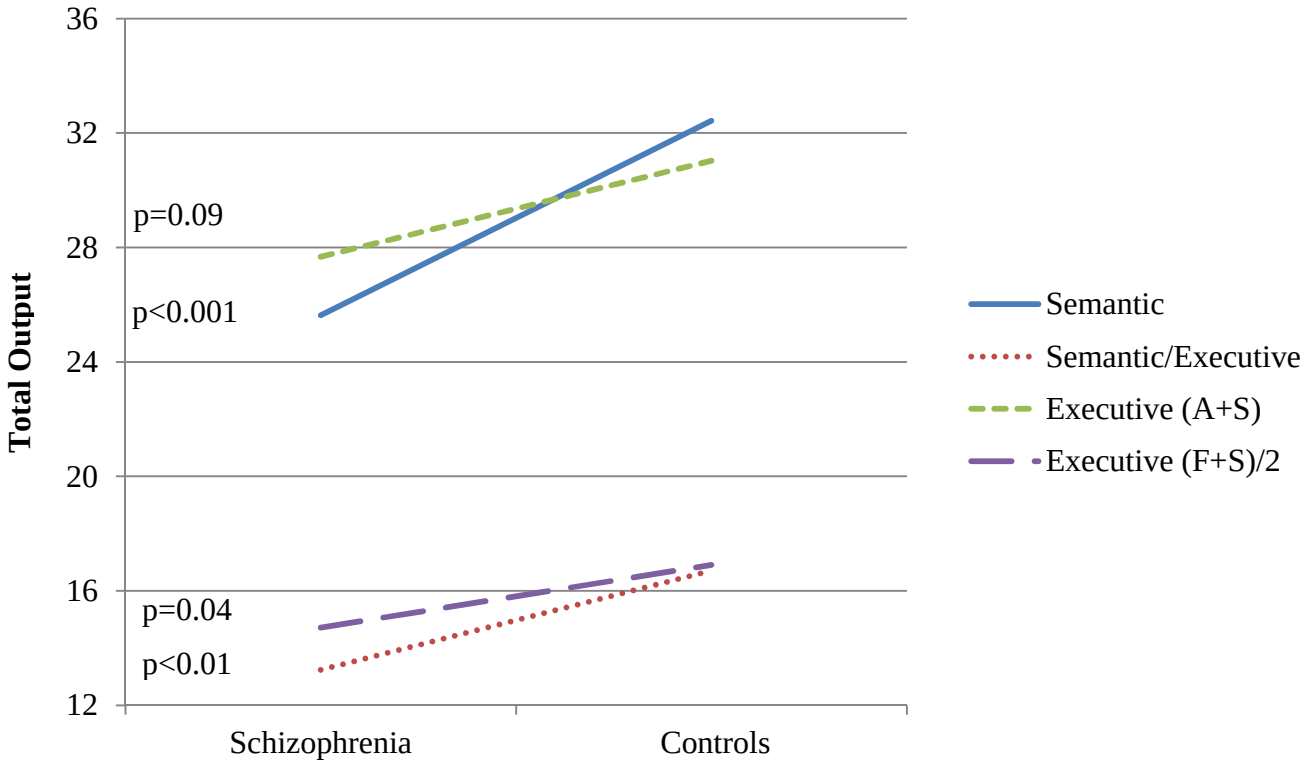

Figure 6.1 Performances across Three Fluency Tasks Comparing Schizophrenia to Controls

6.5.4 Relationship of Fluency to Clinical Variables

Within the SZ group, only semantic fluency performance was significantly correlated with length of illness (r= -0.39, p=0.01). A repeated-measures ANCOVA was run for length of illness to

determine its influence. There was no significant main effect ($F(2, 36) = 3.18$, $p=0.05$), suggesting that the pattern of fluency performance is not changed by length of illness.

Correlations were run between the semantic, semantic/executive and the two calculations for executive fluency tasks, error data and symptoms (i.e. total TLC score, PANSS composite negative score, PANSS delusions specific question). The only significant correlations were between thought disorder (total on TLC measure) and both measures of executive fluency: method (1): $r=0.41$, $p=0.01$, and method (2): $r=0.55$, $p<0.001$. There were no significant relationships between CPZ and current negative symptoms ($r=0.28$, $p=0.09$) or delusions ($r=0.12$, $p=0.47$) on the PANSS.

6.6 Discussion

The results supported all three hypotheses regardless of the method for calculating executive fluency used. (1a) SZ was associated with greater semantic fluency impairment than the control group, (1b) SZ patients demonstrated less seriously impaired performance on the executive task than the semantic task; (2) performance on the semantic/executive task was more impaired in the SZ group than controls, and finally (3) semantic/executive performance was more impaired in SZ than their executive performance.

6.6.1 Hypotheses

Hypothesis (1a) was supported as the SZ group demonstrated significantly more impairment in their semantic fluency output than controls with performance characterized by a 19% reduction in total output. This finding supports the two earlier meta-analyses (Bokat & Goldberg, 2003; Henry & Crawford, 2005).

Regarding hypothesis (1b), the SZ group demonstrated a non-significant reduction in output on the executive task of 10% compared to controls using method 1 (d = 0.34) and a significant reduction in output of 12% using method 2 (d = 0.47). Despite group differences reaching significance using method 2, an examination of the effect sizes for method 2 versus semantic performance (d = 1.04) confirm that semantic fluency performance was more impaired than executive regardless of the method of calculation. This confirms the findings of earlier studies reporting that total output on the executive task is normal (Kubota et al., 2005; Phillips, James, Crow, & Collinson, 2004) or less impaired than semantic fluency output (Bozikas, Kosmidis, & Karavatos, 2005) in SZ.

6.6.2 Animals by size

The SZ group demonstrated a significant 24% reduction in output compared to controls on the semantic/executive task in support of hypothesis (2). Finally, the SZ group demonstrated a greater reduction on the semantic/executive task than the executive only. Using method 1, this hypothesis was supported on the basis that there was no group difference on executive but there was a group difference on the semantic/executive fluency task. Using method 2, effect sizes indicated that executive fluency performance d= 0.47 was not as impaired as semantic/executive, d= 0.73 performance.

In the introduction, the question of whether performance on the semantic/executive task would be driven by semantic or executive function was raised. Analysis controlling for the effects of the executive fluency task on semantic/executive function did not diminish the group differences in semantic/executive performance. This is an incomplete analysis however, as it is possible that the executive skills associated with the executive and the semantic/executive tasks are not the same. The semantic/executive task may put more pressure on the same executive skills required for executive

fluency and/or may require additional executive skills. These possibilities could not be controlled for with the current data. Instead, to determine whether the semantic element of the task was responsible for group differences the two groups were compared on the semantic/executive task whilst controlling for semantic fluency. The findings showed that when the semantic element of the task was controlled for, the group differences disappeared. This confirmed that the SZ performance was driven by the semantic element of the task regardless of whether it also required other executive skills.

6.6.3 Relationship between symptoms and fluency

The different pattern of results reported by Doughty and Done (2009) in their meta-analysis compared to the two earlier meta-analyses (Bokat & Goldberg, 2003; Henry & Crawford, 2005) may have been affected by the symptom profiles of SZ participants. There is evidence of a relationship between thought disorder and fluency (McKenna et al., 1994; Rossell et al., 1999). This was partially supported by the current study, which found a significant relationship between thought disorder and executive errors. This current finding supports the work of previous authors who suggest that thought disorder is related to error performance (Kuperberg et al., 1998). A relationship has also been found between delusions (Goldberg et al., 1998; Spitzer, 1997) and verbal fluency. This relationship was not supported by the current study. Finally, an association between fluency and negative symptoms has been noted (Joyce et al., 1996). Negative symptoms were low in the current study which may explain why this relationship was not replicated. Doughty and Done do acknowledge symptom profile of participants as a potential confound in this research field. The varying symptom profiles between the samples examined in each meta-analysis may have contributed to their discrepant findings in the literature.

The relationship between negative symptoms and fluency might be a particular driving force behind the finding of worse executive than semantic function. Research indicates that there is a relationship between negative symptoms and executive dysfunction (Basso, Nasrallah, Olson, & Bornstein, 1998; Donohoe, Corvin, & Robertson, 2006). Regression analysis has shown that while positive symptoms relate to overall intellectual function, this relationship is stronger for negative symptoms, and there is an additional relationship between negative symptoms and executive function (Basso et al., 1998). Donohoe et al. (2006) found greater executive problems among those with negative symptoms and concluded that such symptoms may well be the expression of executive dysfunction. One of the fluency papers included in Doughty's meta-analysis noted a significant negative relationship between alogia and executive fluency ($r = -0\text{-}30$, $p = 0.04$), while the relationship with semantic fluency did not reach significance ($r = -0\text{-}27$, $p = 0.06$) (Joyce et al., 1996).
Future studies investigating semantic function might consider including all three fluency measures so that both within and between group comparisons might be made. Further examination of the pattern of performance across the fluency tasks should be examined with regard to positive symptoms (especially thought disorder and delusions) and negative symptoms.

6.6.4 Limitations

Normative data and test characteristic information regarding the semantic/executive fluency task is scarce; further research is required so that it might be used as a research tool and possibly incorporated into standard fluency batteries.

6.7 Conclusion

A novel approach was used to clarify the role of semantic fluency in measuring semantic function in SZ. The results support the efficacy of the semantic task as a semantic measure in SZ. Further, they introduce a fluency task that has rarely been used in research before but may well provide further useful information regarding semantic and executive function in a variety of disorders.

CHAPTER 7. SCHIZOPHRENIA: THE RELATIONSHIP BETWEEN LOWER ORDER COGNITIVE SKILLS AND EXECUTIVE FUNCTIONS

DECLARATION FOR THESIS CHAPTER 7

Declaration by candidate:

In the case of Chapter 7, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, data collection, data analysis and writing of manuscript.	90%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Susan Rossell	Supervisor of Erica Neill's PhD. Provided assistance in data analysis and proof reading of the manuscript

Candidates Signature: [redacted] **Date: 14/01/13**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from 2009

Susan Rossell [redacted] **Signature: Date: 14/01/13**

7.1 Chapter Guide

This is the second of three chapters concerned with examining the relationship between executive functioning and other areas of cognition. This chapter consists of an article that is under review with Schizophrenia Research. There is no additional information included in this chapter beyond the submitted article as section 1.2 in Chapter One contains additional information regarding semantic and executive function in schizophrenia.

7.2 Abstract

Executive functioning (EF) impairments are common in schizophrenia. There are two propositions regarding the causes of these impairments: (1) executive impairments are the result of the compounding effects of deficits in lower order cognitive skills (e.g. processing speed, attention) or (2) EF impairments exist in their own right regardless of lower order skills. It is difficult to examine the separable effects of lower order cognitive skills on EF given the overlap required to complete most neuropsychological measures. One battery designed to parcel out the contributions of lower order skills from EF is the Delis-Kaplan Executive Function System (D-KEFS). Inhibition and switching specifically were examined using the D-KEFS versions of the Stroop and Trails task. No group differences in task performance after controlling for lower level skills would provide evidence for a generalised cognitive deficit. Group differences remaining after controlling for these influences would suggest a disproportionate deficit. Results supported both propositions. On both tasks, group differences reflecting slowed reaction time in the schizophrenia group disappeared when lower order skills were controlled for. Differences between groups performance in errors were only evident on the most complex versions of each task with more errors made by the schizophrenia group. These results suggests that (1) both RT and error data are needed to provide a full picture of performance and (2) the relationship between lower order and EF are too complex to provide support for one or the other proposal.

7.3 Introduction

Executive functioning (EF) is impaired in schizophrenia (Bryson, Whelahan, & Bell, 2001; Mahurin, Velligan, & Alexander, 1998; Morice & Delahunty, 1996). EFs describe a range of higher level thinking skills which include, but are not limited to, complex attention, abstract thought, planning/organizing, inhibition and self-monitoring (Baddeley & Hitch, 1974; Delis et al., 2001; Lezak et al., 2004; Luria, 1966; Norman & Shallice, 1986; Stuss & Alexander, 2000). Research suggests that deficits in EFs affect between 40-95% of individuals with schizophrenia (Velligan & Bow-Thomas, 1999). Further, research suggests that these deficits exist prior to first episode (Lencz et al., 2006; Morey et al., 2005; Simon et al., 2007), are present between episodes (Townsend, Malla, & Norman, 2001), and that milder executive problems are present in first degree relatives (Snitz, MacDonald, & Carter, 2006; Szoke et al., 2005).

7.3.1 Theories of Executive Function

Deficits in EF significantly predict long term outcome (Reed et al., 2002; Velligan & Bow-Thomas, 1999) and as a result, EF is often a key element in contemporary neurocognitive models of psychosis (Savla et al., 2011). Characterising EF impairments is difficult given the relationship between these skills and lower order contributions (Johnson-Selfridge & Zalewski, 2001) and this is made more complex again in schizophrenia given the wide ranging cognitive problems associated with this disorder (Heinrichs & Zakzanis, 1998). There are two opposing views regarding the nature of EF deficits in SZ. One proposes that EF deficits are a hallmark of psychosis in their own right, this proposition will be referred to as the 'disproportionate deficit' model (Barch et al., 2009). While others suggest that rather than a specific deficit in EF, schizophrenia is characterised by lower level

impairments which cause difficulties in performing higher level tasks, this is referred to as the ‘general deficit’ model (Dickinson & Gold, 2008; Laws, 1999).

Support for the disproportionate deficit model comes from research finding that EF is more significantly impaired than other areas of cognition (Velligan & Bow-Thomas, 1999) and EF has been found to be impaired even if general IQ is intact (Morice & Delahunty, 1996; Weickert et al., 2000). Additionally, if working memory is counted as an executive task, then there is evidence that even when immediate memory span is intact (digits forwards), it is only the higher level working memory component of the same task that differentiates schizophrenia from control groups (digits backwards) (Stone, Gabrieli, Stebbins, & Sullivan, 1998). Deviating somewhat, but not contradicting this model, are the findings that disproportionate EF occurs only in those individuals with a predominantly negative symptom profile (Bryson et al., 2001; Donohoe, Corvin, et al., 2006; Mahurin et al., 1998).

Meta analytic results have been used to support the general deficit proposition (Laws, 1999). An examination of 29 studies utilising the Wisconsin Card Sorting test led authors to the conclusion that when lower order cognitive skills are accounted for, there is no disproportionate EF deficit (Laws, 1999). Research using regression analysis found that even accounting for the fact that EF is heterogeneous in SZ, general IQ and processing speed still underlie these deficits (Raffard & Bayard, 2012). An examination of cognitive profiles of schizophrenia participants found that EF is not the most significantly impaired area of cognition in schizophrenia, with attention equally impaired (Kremen et al., 2001).

7.3.2 Confounds in the Literature

It appears that there are numerous reasons for the contradictions in the literature. Two important contributing factors include (1) the heterogeneity of schizophrenia, and associated variations in cognitive profiles; and (2) the fact that EFs do not reflect a single skill. As such, it may be that some EF deficits are explained by lower order problems, whilst others reflect executive specific impairments (Raffard & Bayard, 2012).

Determining the separable effects of lower order cognitive skills, such as basic attention and processing speed, on EF is difficult given the overlap in skills required to complete most neuropsychological measures (Dickinson & Gold, 2008). One attempt to separate the contributions of various skills is offered by the Delis Kaplan Executive Function System (D-KEFS) (Delis et al., 2001). This cognitive battery includes both classic and new neuropsychological measures designed to tease out the effects of lower order cognitive skills from EF. The purpose of the current paper is to examine the performance of a schizophrenia sample on two of these measures, the D-KEFS versions of the Stroop and the Trails task, to see what skills actually determine performance on these tasks in a stable chronic schizophrenia group.

The traditional Stroop task is a common measure of EF in schizophrenia (Dickinson, Ramsey, & Gold, 2007; Johnson-Selfridge & Zalewski, 2001) along with variations examining single trial performance (Barch, Carter, & Cohen, 2004; Barch, Carter, Hachten, Usher, & Cohen, 1999). These tasks allow for an examination of reading speed, colour identity speed and inhibition. The traditional Stroop task also provides a measure of processing speed. This is provided by subtracting the time taken to read the colour words and identify the colours away from performance on the inhibition part of

the task; and as such, is already able to isolate some lower order cognitive factors from higher level ones. The D-KEFS version provides another level of sophistication by including a fourth task which measures inhibition and switching, and provides calculations that allow the examiner to differentiate the roles of reading, and colour naming speed, from inhibition, and from switching. Both RT and error data are collected and examined for this version.

The traditional Trails B task, which is also used to measure EF in schizophrenia (Hughes et al., 2003; Mahurin et al., 2006), provides a measure of working memory and attention switching. The traditional Trails task has two parts. The first provides a combined measure of scanning, processing speed and letter sequencing. The second part requires the additional skill of switching. Schizophrenia studies utilising the Trails task generally do not report error data instead focusing on RT separately for A and B (Erwin, Turetsky, Moberg, Gur, & Gur, 1998; Hughes et al., 2003) or using a combination score calculated as A minus B (Smith et al., 1998; Wykes, Reeder, Corner, Williams, & Everitt, 1999). One paper examining both reported that while Trails B RT data related to visual scanning, Trails B error rates were related to mental tracking and working memory indicating the unique importance of each (Mahurin et al., 2006). The D-KEFS version breaks these skills down further by including five different tasks. The first measures scanning, the second number sequencing, the third letter sequencing, the fourth the traditional Trails B condition (switching between numbers and letters), and the fifth a processing speed task. Both RT and error data are collected and examined for this version.

7.3.3 D-KEFS Battery

There are multiple studies evaluating the D-KEFS battery. The authors of the battery (Delis, Kramer, Kaplan, & Holdnack, 2004) suggest that it is associated with good reliability and validity

including good inter-rater and test-retest reliability. Other papers have argued that the reliability is not particularly high, but have dismissed this as a serious issue on the basis that EF are multifaceted leading to greater variability (Shunk, Davis, & Dean, 2006). Another study found that the DKEFS sorting task was better at discriminating between multiple sclerosis and controls than the Wisconsin Card Sorting Task (Permenter et al., 2007). Others have found that the DKEFS, particularly the Trails tasks, have good ecological validity (Mitchell & Miller, 2008). A more recent review examining administration, scoring, interpretation, test construction, standardization, and technical adequacy concluded that this battery is suitable and useful as both a clinical and research tool (Homack, Lee, & Riccio, 2005). Previous studies have used the D-KEFS to examine executive function in schizophrenia (Clark, Warman, & Lysaker, 2010; Lysaker et al., 2008). They both failed to take advantage of the additional contrast measures that will be examined in the current study.

Given that (1) the contrast scores from the D-KEFS have not been published in a schizophrenia cohort before; and (2) there is reasonable evidence for both the disproportionate deficit and the general deficit arguments, specific directional hypotheses are not made. If there are no group differences on higher level functions when lower level functions are accounted for using contrast scores, this will provide evidence for the general deficit proposition. If, on the other hand, group differences remain, this will provide evidence for the disproportionate deficit model. This study aims to examine these two models using the DKEFS Stroop and Trails.

7.4 Methods

7.4.1 Participants

Forty individuals with a diagnosis of schizophrenia participated in the current study. Thirty six of these participants were outpatients who responded to advertising in supported accommodation and community mental health services; and four were inpatients at the Alfred Hospital Melbourne who were willing to participate with their consulting psychiatrist's permission. Diagnosis and symptom profile was investigated using the Structured Clinical Interview Diagnostic (SCID) (First et al., 1997) and current symptoms were evaluated using the Positive and Negative Symptoms Schedule (PANSS) (Kay et al., 1987). To be eligible to participate, all schizophrenia participants needed to score >40 but <80 on the total PANSS score to ensure that all participants were mild to moderately unwell at the time of testing, but not severe, enabling them to provide consent and understand all study instructions (Leucht et al., 2005). Forty two healthy controls were recruited from advertisements around the Alfred Hospital and Monash University. They were screened for psychiatric illness using the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962). All participants were included on the basis that they had no significant head injury history, no neurological illnesses and no current substance dependence. Healthy controls specifically were excluded if they had any history of psychiatric illness.

7.4.2 Procedure

All participants were administered both the Trails tasks and the Stroop task on the same day. Tasks were administered by a trained researcher (EN) following the instructions specified in the D-KEFS manual.

Stroop: The four versions of the Stroop were administered in the order outlined in the D-KEFS manual: colour, word, inhibition and inhibition/switching. For each version, reaction times (RT) in seconds and number of errors were recorded. The RT scores calculated included speed of colour naming (condition 1), word reading (condition 2), inhibition (condition 3), inhibition/switching (condition 4) and combined colour naming and reading speed (conditions 1 + 2). Primary contrast measures calculated included inhibition/switching vs. combined naming + reading (condition 4 scaled – conditions 1 + 2 scaled) and inhibition/switching vs. inhibition (condition 4 scaled – condition 3 scaled).

Trails: The five versions of the D-KEFS trails were administered in numerical order as instructed by the D-KEFS manual. The response sheets were larger than traditional Trails tasks. Traditional tasks are generally presented on A4 sized paper (297mm x 210mm) while the D-KEFS response sheets are twice as large on A2 sized paper (594mm x 420mm) providing more stimuli. The benefit of this is that a longer task provides greater variability in RT and also increases the likelihood of errors which helps to avoid a floor effect. Trails 1 is a measure of visual scanning and requires participants to scan a page of numbered circles and put a dash through all the 3s they can find as quickly as possible. Trails 2 requires participants to join numbers sequentially and Trails 3 requires them to joins letters sequentially. Trails 4 is the same as Trails B requiring switching between letters and numbers. Finally, Trails 5 is a motor sequencing task in which participants must trace over a dotted line that joins together empty circles.

RT performance on both tasks was compared using scaled scores to provide consistency in the results as all contrast measures were calculated based on scaled scores, and it assists in comparison

with normative data and across measures[3]. Error data on the other hand, was examined as raw data as no contrast measured have been created for these tasks.

7.4.3 Statistical Analysis

Demographic details (gender, age, education and premorbid IQ) were compared between the schizophrenia and control group. Any significant group differences were correlated with performance on the two tasks. If there is a significant group difference on a variable and it correlates with cognitive performance, it will be controlled for statistically. In addition, clinical data will be correlated with the task scores to determine whether there is any relationship between task performance and symptoms. Based on previous research examining Stroop performance in schizophrenia (Woodward, Ruff, Thornton, Moritz, & Liddle, 2003), both RT and error data were correlated with the negative subscale of the PANSS.

Multiple independent t-tests were run to determine whether there were group differences in performance across the main and contrast measures for each task. To control for multiple comparisons, the significance level was set to 0.01.

7.5 Results

7.5.1 Demographic comparisons

Age was the only significant difference, with schizophrenia participants older (see Table 7.1) ($M=41.05 \pm 10.76$) than the controls ($M=33.20 \pm 12.5$; $t(80) = -3.05$, $p<0.001$). There was no need to control for this variable when examining RT data as the scaled scores from the D-KEFS are age

[3] NB there was no difference in direction or significance of any analysis if raw RT scores were used.

corrected The D-KEFS does not provide scaled scores for all error data. As such, 'age' was correlated with raw error data for both the Stroop and the Trails tasks. There were no significant correlations between error performance and age in controls or the schizophrenia group on either task. As such, age was not co-varied for in the following analyses. Finally, the negative subscale of the PANSS did not correlate with RT or error performance on the Stroop or Trails tasks.

Table 7.1 *Demographic and Clinical Data*

	Schizophrenia (N=42)	Controls (N=40)
Male/Female	25/17	17/23
Age (years)*	41.05 (10.76)	33.2 (12.5)
Education (years)	15.14 (4.01)	16.2 (2.56)
WTAR IQ	99.81 (14.35)	103.2 (9.25)
PANSS (Positive)	15.52 (4.52)	
PANSS (Negative)	11.43 (3.42)	
PANSS (General)	28.29 (8.84)	
PANSS (total)	55.24 (14.22)	
Length of illness	18.1 (10.15)	
CPZ mean dosage	485.22 (348.11)	

7.5.2 Stroop Tasks

7.5.2.1 RT data

As shown in Table 7.2 there were significant group differences in colour naming ($t(79) = 2.62$, $p=0.01$), reading ($t(79) = 2.68$, $p=0.01$), inhibition ($t(79) = 2.86$, $p=0.01$) and inhibition/switching ($t(79) = 3.66$, $p<0.00$). An examination of the contrast measures shows that there were no group differences when inhibition/switching was compared to inhibition only ($t(79) = 0.34$, $p=0.74$) or when it was compared to a combination of reading/colour naming ($t(79) = 1.56$, $p=0.12$).

7.5.2.2 Error data

There were no significant differences in errors to word reading (t (79) = -0.57, p=0.57), colour reading (t (79) = -0.83, p=0.41) or inhibition (t (79) = 0.59, p=0.56). There was however a significant group difference on inhibition/switching (t (79) = -2.67, p=0.01).

Table 7.2 *Stroop Reaction Time and Accuracy Data*

Scaled RT scores (M=10, SD=3)	Group	Mean (SD)	Sig.
Colour Identification	Controls	9.77 (1.94)	p= 0.01
	Schizophrenia	8.17 (3.31)	
Word Reading	Controls	10.36 (2.63)	p= 0.01
	Schizophrenia	8.66 (3.03)	
Inhibition	Controls	11.03 (2.58)	p= 0.01
	Schizophrenia	9 (3.63)	
Inhibition and Switching	Controls	10.44 (1.9)	p<0.001
	Schizophrenia	9.54 (3.67)	
Inhib/Switch controlling for Inhibition	Controls	8.39 (3.49)	p= 0.74
	Schizophrenia	8.64 (3.19)	
Inhib/Switch controlling for colour and word reading	Controls	9.9 (1.85)	p= 0.12
	Schizophrenia	8.88 (3.67)	
Raw Error Scores			
Colour Identification Errors	Controls	0.62 (0.94)	p= 0.57
	Schizophrenia	0.74 (0.99)	
Word Reading Errors	Controls	0.41 (0.79)	p= 0.41
	Schizophrenia	0.57 (0.94)	
Inhibition Errors	Controls	0.72 (1.03)	p= 0.56
	Schizophrenia	0.59 (0.97)	
Inhibition/Switching Errors	Controls	0.67 (0.77)	p= 0.01
	Schizophrenia	1.34 (1.39)	

7.5.3 Trails Tasks

7.5.3.1 RT data

There were significant group differences on all five versions of the Trails task, characterised by worse performance in the schizophrenia group (see Table 3 for means). Trails 1: ($t(79) = 4.08$, $p<0.001$), Trails 2: ($t(79) = 5.47$, $p<0.001$), Trails 3: ($t(79) = 6.70$, $p<0.001$), Trails 4: ($t(79) = 4.89$, $p<0.001$), Trails 5: ($t(79) = 0.32$, $p<0.001$). The significant group difference on Trails D (the switching condition) remained even after controlling for letter and number sequencing ($t(79) = -3.15$, $p<0.001$). The switching difficulty disappeared however, when scanning ($t(79) = 0.81$, $p=0.43$) and motor speed were controlled for ($t(79) = 0.32$, $p=0.75$).

7.5.3.2 Error data

For the error data, there were no significant group differences on Trails 1 ($t(79) = -0.76$, $p=0.45$), Trails 2 ($t(79) = -0.96$, $p=0.34$), Trails 3 ($t(79) = 0.05$, $p=0.96$) or Trails 5 ($t(79) = -.90$, $p=0.37$). The only group difference was in errors on the most complex Trails 4 (the switching task) ($t(79) = -2.05$, $p=0.05$).

Table 7.3 *Trails Reaction Time and Accuracy Data*

Scaled RT scores (M=10, SD=3)	Group	Mean (SD)	Sig.
Trails A (Visual Scanning)	Controls	10.87 (2.29)	p<0.001
	Schizophrenia	8.60 (2.71)	
Trails B (Number Sequencing)	Controls	12.28 (1.81)	p<0.001
	Schizophrenia	8.83 (3.53)	
Trails C (Letter Sequencing)	Controls	12.36 (1.89)	p<0.001
	Schizophrenia	8.40 (3.20)	
Trails D (Switching between Numbers and Letters)	Controls	11.95 (1.36)	p<0.001
	Schizophrenia	9.12 (3.37)	
Trails E (Motor Speed)	Controls	11.97 (1.56)	p<0.001
	Schizophrenia	9.43 (2.95)	
Switching vs. Number/Letter	Controls	11.23 (2.91)	p<0.001
	Schizophrenia	8.98 (3.31)	
Switching vs. Motor Speed	Controls	9.97 (1.66)	p= 0.75
	Schizophrenia	9.76 (3.84)	
Switching vs. Visual Scanning	Controls	11.03 (1.72)	p= 0.42
	Schizophrenia	10.55 (3.39)	
Raw Error Scores			
Trails A (Visual Scanning)	Controls	0.03 (0.16)	p= 0.45
	Schizophrenia	0.07 (0.34)	
Trails B (Number Sequencing)	Controls	0 (0)	p= 0.34
	Schizophrenia	0.07 (0.46)	
Trails C (Letter Sequencing)	Controls	0.03 (0.16)	p= 0.96
	Schizophrenia	0.02 (0.15)	
Trails D (Switching between Numbers and Letters)	Controls	0.36 (0.81)	p=0.05
	Schizophrenia	0.90 (1.51)	
Trails E (Motor Speed)	Controls	0.03 (0.16)	p=0.37
	Schizophrenia	0.12 (0.63)	

7.5.3.3 Speed/Accuracy Trade off

There were significantly more errors for the Trails switching component and for the inhibition/switching component of the Stroop. The possible contribution of a speed/accuracy trade off was investigated for these conditions. There was a significant positive correlation between RT and errors on the Trails switching task (r= 0.45, N=39, p>0.00) indicating that as errors increased, so did

RT indicating no speed/accuracy trade off. There was no significant correlation between Stroop inhibition/switching RT and error scores (r= -0.07, N=39, p= 0.68) also indicating no speed/accuracy trade off.

7.6 Discussion

This study investigated the contribution of lower level cognitive abilities on participant's performance of executive tasks measuring inhibition and switching.

The results of this study suggest that lower order cognitive skills contribute significantly to EF deficits in inhibition and switching in schizophrenia, but do not account for them completely. The RT data support the GD model, with schizophrenia deficits on all the lower order tasks and subsequently, no significant differences between groups when contrast scores from the DKEFS were compared. An examination of the raw error scores shows that there are no group differences on those versions of the task that rely only on lower order cognitive skills. Instead, the group differences emerge only on the most complex/executive versions of each of the tasks supporting the DD models assertion; that is, inhibition and switching EF deficits exist above and beyond the contributions of lower order skill deficits. These results indicated that error data may be more sensitive to inhibition and switching deficits while RT data captures the contribution of lower order skills. It might be argued that the use of raw scores and the lack of contrast scores for errors make the RT and error data difficult to compare. Further, it might be suggested that errors on higher level versions of the task could be attributed to lower order skills. Given the lack of group differences in errors on the more basic versions of each task however, this is unlikely. Firstly, there were no group differences on error on the lower level versions of the task, therefore, difficulties on these levels are unlikely to have compounded and resulted in the

higher level difficulties shown. Secondly, given that raw RT data supported the findings of the scaled RT data it is reasonable to compare the RT and error data.

Comparing the current results to previous literature is confounded by differences in task type and analysis techniques. Those schizophrenia studies investigating Stroop performance specifically often utilise a single trial performance format which includes a neutral baseline for comparison (Barch et al., 2004; Barch et al., 1999; Perlstein, Carter, Barch, & Baird, 1998). Despite differences in administration, these studies confirm the importance of examining error data citing normal RT interference levels in the face of greater errors. The study by Mahurin (2006) using the traditional Trails task found that the schizophrenia group were slower on A and B and made significantly more errors on B only providing support for the current findings.

Unlike some previous literature (Bryson et al., 2001; Donohoe, Clarke, et al., 2006; Mahurin et al., 1998) there was no relationship found between negative symptoms and cognitive performance on the Stroop or Trails. All three previous studies found a significant relationship between those with a 'deficit' syndrome pattern of performance, more negative symptoms, and poor performance. Additionally, Mahurin (1998) reported a relationship between attention and cognitive disorganisation and between verbal memory and reality distortion. Differences between the current study and the findings of previous studies may stem from the reliance of different symptom scales (Brief Psychiatric Rating Scale) and different measures of executive function (Wisconsin Card Sort, an experimental Stop Signal measure of inhibition).

Future studies should consider using more acutely psychotic schizophrenia participants to see whether (1) symptoms do interact with performance and (2) because more acute psychosis may be associated with higher error rates which can then be related to executive performance more reliably.

The advantages of this paper stem from the use of valid and reliable measures with extensive norms. Further, both RT and error data were recorded providing a more fine grained examination of EF function.

CHAPTER 8. THE RELATIONSHIP BETWEEN SCHIZOPHRENIA SYMPTOMS AND COGNITIVE FUNCTION

DECLARATION FOR THESIS CHAPTER 8

Declaration by candidate:

In the case of Chapter 8, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, data collection, data analysis and writing of the chapter.	90%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Susan Rossell	Supervisor of Erica Neill's PhD. Provided assistance in data analysis and proof reading of the chapter

Candidates Signature: [redacted] **Date: 14/01/13**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from 2009

Susan Rossell [redacted] **Signature:** **Date: 14/01/13**

8.1 Chapter Guide

This is the third of three chapters examining executive function in schizophrenia. This chapter has not been written up as an article.

8.2 Introduction

The purpose of the current chapter is to explore firstly, the relationship between severity of formal thought disorder (FTD) and other relevant variables in this thesis; including delusions, semantic memory and executive functions. This is then followed by an examination of the relationship between the severity of delusions and semantic memory and executive functions

8.2.1 Formal Thought Disorder and Delusions

The possibility that the symptoms of delusions and FTD are related was proposed by Bleuler (1911/1950). He suggested that 'loose associations' (a description of FTD) would encourage the development of abnormal thoughts and ideas (Mortimer et al., 1996). Other authors investigating delusions (Cutting & Murphy, 1988; Frith, 1992; McKenna, 1991; Rossell et al., 1999) and those investigating FTD (Gouzoulis-Mayfrank et al., 2003; Kerns & Berenbaum, 2002; Spitzer, Braun, Hermle, & Maher, 1993; Spitzer, Braun, Hermle, & Maier, 1993) have both proposed a link between these symptoms and impairments in semantic memory. There is data to suggest that the two are interconnected, with research describing FTD, delusions and abnormalities in real world knowledge (semantic memory) as symptoms of a more general 'thought disorder' (Cutting & Murphy, 1988). Other authors have reported significant correlations between the two symptoms (Mortimer et al., 1996) although, this relationship is not always found (McKenna et al., 1994).

8.2.2 Formal Thought Disorder and Semantic Memory

The relationship between semantic memory and FTD was discussed in detail in Chapter One. To summarise again briefly, FTD is thought to be the result of an excessive spread of activation or a failure of inhibition in the semantic memory system. This leads to a difficulty in focused thought and language resulting in FTD symptoms (Spitzer, 1997).

8.2.3 Formal Thought Disorder and Executive Function

While there is significant evidence that FTD is related to a semantic deficit, there is also evidence that FTD is associated with executive dysfunction (Barrera et al., 2005; Stirling et al., 2006). In a study by Barrera and colleagues (2005), authors compared a FTD and a no FTD group of schizophrenia participants on four semantic (Camels and Cactus Test, the Concrete and Abstract Word Synonym Test, the British Picture Vocabulary Scale and the Graded Naming Test) and four executive tasks (the Hayling and Brixton, the Modified Six Elements Test and the Cognitive Estimates Test). They found that the FTD group were significantly more impaired than the no FTD group on all four executive measures and one of four semantic tests[4]. Using a correlational approach, Stirling (2006) found a significant relationship between FTD and both semantic (semantic fluency, speed comprehension test and the Quick test) and executive function (including both the Stroop and Trails task). Higher levels of FTD were associated with worse performance in both areas of cognition.

[4] It is important to add that one of the executive tasks was the 'cognitive estimates' tests which has a significant semantic element. As such, semantic memory may well have contributed to that impaired performance as well. Further, two of the semantic tasks were 'naming' tasks using for aphasic or demented patients. As such, they were likely too easy for a schizophrenia sample.

8.2.4 Delusions and Semantic Memory

The proposal of a relationship between delusions and semantic memory has not been explored as widely (McKenna, 1991; Rossell et al., 2008; Rossell et al., 1999). To briefly recap the discussion from Chapter One; schizophrenia is associated with abnormal perception and cognition. These abnormalities then influence the structure of semantic memory. Abnormalities in the structure of semantic memory are likely to influence thought processes relating to meaning which can lead to and maintain delusional ideas (McKenna, 1991).

There is one research paper that examined the relationship between semantic memory and delusions using the semantic fluency task (Rossell et al., 1999). These authors found that the more delusional participants demonstrated a greater impairment in semantic fluency output than did their non-deluded counterparts. This particular paper is relevant as semantic fluency data was collected for this thesis (see Chapter Six). Therefore, specific hypotheses will be made with regards to the relationship between delusions and semantic fluency performance.

8.2.5 Delusions and Executive Function

The relationship between delusions and executive function is often implied but not specified. For example, the suggestion of a relationship between the two is made in theories of delusion formation including probabilistic reasoning bias which, as its name suggests, includes the theory that reasoning (an executive skill) is impaired leading to the formation and maintenance of delusions (Garety et al., 1991). Others refer to a difficulty in critically evaluating evidence, also an example of an executive skill (Langdon & Coltheart, 2000). Some authors have proposed a link between frontal damage (an area highly connected with executive function) and the development of delusions (Benson & Stuss,

1990). Frith and Done (1989) suggested a link between frontal function and the specific delusion that movements are controlled by an external force. Others find no evidence of greater impairment in executive function in delusional versus non-delusional individuals (using the Wisconsin Card Sorting Test) (Kremen, Seidman, Goldstein, Faraone, & Tsuang, 1994). In fact, it is often the case that delusions cannot be specifically linked to poor executive functioning (using the sentence arrangement test from the WAIS-R) (Berenbaum, Kerns, Vernon, & Gomez, 2008). Some authors suggest that abnormal perception is required, in addition to other cognitive deficits, to facilitate the formation of delusions (Langdon & Coltheart, 2000). There is still some argument regarding which perceptual deficits are necessary to initiate delusion formation and also some evidence to suggest that some delusional individuals do not demonstrate any clear impairments in perception (Bell, Halligan, & Ellis, 2006). In response to this, other authors have suggested that the additional deficit need not be perceptual and instead, may stem from motivational, desires or defensive behaviours (McKay, Langdon, & Coltheart, 2005).

Current hypotheses to be tested:

With regards to FTD, it is hypothesised that (1) FTD severity will correlate positively with delusions and (2) the higher the FTD score, the slower performance will be on semantic tasks. Finally, the only study including executive tasks incorporated in the current chapter was the work of Stirling (2006) which included the Stroop and Trails task. They found that the schizophrenia group were slower on both tasks Therefore, the final hypothesis is (3) FTD will be associated with slowing on both the Stroop and Trails task.

With regards to delusions, it is hypothesised that delusions will be negatively correlated with semantic function. That is, with regards to semantic priming performance, it is hypothesised that on priming tasks associated with poor performance in schizophrenia, the higher the delusions, the more impaired the semantic performance (measured as longer RTs). Further, with regards to semantic fluency, it is predicted that as delusion severity increases, semantic fluency output will decrease.

The evidence for a relationship between delusions and executive functions are less clear. Further, there is the possibility that the relationship between delusions and executive functions may be mediated by perceptual or psychological variables which have not been collected in this thesis. As such, no specific hypotheses are made in this regard.

8.3 Data Analysis

8.3.1 Formal Thought Disorder Analysis

In Chapter One, Section 1.3.1, the importance of treating positive and negative FTD separately was discussed. This has been taken into account and FTD scores were broken down into positive and negative thought disorder based on a published factor analysis (Harvey et al., 1992). Harvey and colleagues found that negative FTD was best measured by adding together the items 'poverty of speech' and 'poverty of content of speech'. Positive FTD included a greater number of items: pressure of speech, tangentiality, derailment, incoherence, circumstantiality and loss of goal. The global positive and negative FTD scores were subsequently correlated with executive and semantic performance.

8.3.2 Correlations

Relationships between semantic and executive function, thought disorder and delusions were examined using Correlations. To correct for multiple comparisons, significance was adjusted to p=0.01. Prior to conducting these correlations, skewness was calculated to determine the most appropriate correlations to run. Specifically, Pearson's correlations will be used if skewness is within normal range and Spearman's correlations will be run if the skewness is not normal (Miller & Chapman, 2001).

8.3.3 Executive Functions Analysis

With regards to the executive tasks, correlations were run between those executive tasks that have (1) not been investigated thus far in this thesis (digits backwards and mazes) or (2) were found to tap executive functions after controlling for lower order cognitive abilities in Chapter Seven (Stroop Inhibition/Switch errors and Trails D errors).

8.3.4 Semantic Memory Analysis

In terms of semantic tasks, correlations were run between symptoms and RT to related and unrelated pairs from the direct 250msec priming task as this was associated with no priming in the schizophrenia group. In addition, RT to related and unrelated pairs from the indirect explicit task (Objects task) were investigated. The decision to run the correlation separately for the related and unrelated pairs, instead of the priming scores, is so fine grained relationships can be investigated (i.e. group differences could be due to abnormal reaction times to either related or unrelated pairs or both). The only correlations with errors that were run were between symptoms and errors to related and

unrelated pairs separately for the indirect explicit tasks, as the 450msec group demonstrated more errors in this condition.

8.3.5 Fluency Analysis

Finally, t-tests were run to determine whether deluded schizophrenia participants differed from non-deluded participants on semantic and phonemic fluency. Participants were deemed to be delusional if they had a score of three or higher on the PANSS. This was the chosen cut-off as a score of two reflects 'questionable pathology' whilst a score of three reflects the presence of delusions.

8.4 Results

8.4.1 Formal Thought Disorder Analysis

The distribution of delusions and thought disorder ratings (separate for positive and negative FTD) were examined and skewness was calculated. There was significant skew for positive (2.91, $p>0.001$) and negative (2.12, $p>0.001$) FTD ratings. Levels of FTD were low in the current sample. Thirty one schizophrenia participants had a total FTD rating of three or less and only eleven had a score higher than this. While there is no definitive cut off for analysis, after establishing the extreme skewing of the current data and the small number of participants demonstrating FTD, it was decided that correlations between FTD, semantic memory and executive function would not provide valid results. Therefore, the remainder of this results section is devoted to the relationship between delusions and cognition. There was still a significant skewing for the delusion ratings (0.14, $p=0.01$). This was not nearly as severe as the skew found when examining the FTD data. Further, a significant number of participants demonstrated some degree of delusional thought so it was deemed appropriate to conduct correlational analysis on the delusional data. Spearman's correlations were used as this method of

analysis is more robust against the effects of skewing than the more traditionally used Pearson's correlations (Hauke & Kossowski, 2011).

8.4.2 Descriptive Analysis

In addition, descriptive analysis was run to provide information regarding the demographic and symptom profile of the schizophrenia group (see Table 8.1).

Table 8.1 *Schizophrenia Symptom Profile*

Schizophrenia (N=42)	
Male/Female	25/17
Age	41.05 (10.76)
Total Years of Education	15.14 (4)
WTAR Scaled Score	99.81 (14.35)
Length of Illness	18.10 (10.15)
CPZ Equivalent	485.22 (348.11)
TLC (Positive)	1.12 (2.47)
TLC (Negative)	0.55 (1.04)
PANSS (Positive)	15.52 (4.52)
PANSS (Delusion)	3.69 (1.47)
PANSS (Negative)	11.43 (3.42)
PANSS (General)	28.29 (8.84)
PANSS (total)	55.24 (14.22)

CPZ= Chlorpromazine Equivalents
PANSS = Positive and Negative Syndrome Scale

8.4.3 Relationship between Delusions and Semantic memory performance

Spearman's correlations between delusions and a number of select semantic memory variables are presented in tables below (see Table 8.2 and 8.3).

Table 8.2 *Spearman's Correlations Between Delusions and Semantic Function: Reaction Time (250msec Group)*

	Delusions	Implicit Direct 250 Related (N=19)	Implicit Indirect 250 Unrelated (N=19)	Explicit Indirect Related (N=41)	Explicit Indirect Unrelated (N=41)
Implicit Direct 250 Related (N=19)	-0.01	1			
Implicit Indirect 250 Unrelated (N=19)	-0.08	0.91*	1		
Explicit Indirect Related (N=41)	-0.16	0.51*	0.58*	1	
Explicit Indirect Unrelated (N=41)	-0.04	0.68*	0.59*	0.67*	1

*p<0.01

Table 8.3 *Spearman's Correlations Between Delusions and Semantic Function: Accuracy (450msec Group)*

	Delusions	Explicit Indirect Related (N=19)	Explicit Indirect Unrelated (N=19)
Explicit Indirect Related (N=19)	-0.08	1	
Explicit Indirect Unrelated (N=19)	-0.06	0.39	1

*p<0.01

8.4.5 Comparison between Deluded and Non-Deluded Participants on Fluency Performance

Schizophrenia participants were compared on semantic and phonemic fluency based on degree of delusion. There were no group differences (comparing deluded and non-deluded subtypes) on any

of the relevant demographic variables: length of illness (t=0.34, p=0.74), WTAR scaled score (t=0.89, p=0.38), age (t=0.40, p=0.69) and Chlorpromazine equivalents (t=0.22, p=0.83) (see Table 8.5). T-tests were run to determine whether semantic fluency performance was different between deluded and non-deluded participants. T-tests showed that the deluded group (M=25.57 ± 7.03) did not differ from the non-deluded group (M=25.70 ± 7.39) on semantic fluency (t=0.06, p=0.96). There was also no difference between the deluded (M=41.52 ± 14.09) or non-deluded group on phonemic fluency (M=36.75 ± 13.83; t=-1.09, p=0.28).

Table 8.4 *Demographics Comparing Deluded versus Non-Deluded Participants*

	Deluded Mean (SD)	Non-Deluded Mean (SD)
Male/Female	13/9	12/8
Length of Illness	18.68 (11.81)	17.59 (8.72)
WTAR scaled score	101.90 (14.70)	97.91 (14.09)
Total Years Education	15.16 (4.30)	15.13 (3.78)
Age	41.75 (12.29)	40.41 (9.40)
Chlorpromazine Equivalent	498.12 (449.44)	472.98 (225.11)

8.5 Discussion

The relationship between FTD, delusions and cognitive measures could not be examined due to the low levels of FTD exhibited by schizophrenia participants and the extreme skewing of the available data. As such, the discussion will focus solely on the hypotheses relating to delusions.

There were no significant correlations between delusions and semantic function across any of the chosen semantic tasks. This does not support the hypothesis put forward. The study by Rossell (1999) concluded that performance on the semantic fluency task was more impaired among deluded participants compared to non-deluded participants. They found a two way interaction between group and fluency only at a trend level (0.07) and further explored this using more fine grained analysis to discover that the deluded group were more impaired on the semantic task. Further, the study by Rossell included three semantic and three phonemic categories; and found that the deluded group differed on two of the three categories. In summary, the author used quite specific analyses and found subtle differences between groups. It may be that a simple t-test between only one semantic and one phonemic category is not sufficient to detect such subtle group differences. Equally, it may be that when semantic and phonemic tasks are matched on discriminating power, inflated differences between groups are eliminated. There were also differences in ratings of delusions. The Rossell study used SAPS scores for current delusions, and the current thesis used the delusion rating from the PANSS. There are differences between the two measures with the SAPS including questions regarding delusions of jealousy. It may therefore provide a more fine grained analysis of delusions than the PANSS. The length of illness for the Rossell group was between 10-12 years whilst it was between 17-19 years in the current study. It is not clear whether this difference in length of illness would actually effect the difference between deluded and non-deluded participant performance but it is possibile that this had some kind of effect.

No specific hypotheses were made with regard to the relationship between delusions and executive function. This was due to the mixed literature, and the suggestion that any such relationship

is probably mediated by factors not taken into account in the current thesis. The result suggested that there was no relationship between the chosen executive tasks and the presence of delusions. While it is possible that the relationship was masked by our failure to collect relevant perceptual and psychological data, it may also be that the choice of executive tasks was inappropriate. The results of Kremen (1994) found no relationship between delusions and digits backwards, nor did the current study. Frith and Done (1989) used a motor task that required error monitoring when they noted a difference in performance between delusional and non delusional schizophrenia participants. The Trails D and Stroop inhibition/switching errors seem reasonable comparison tasks to the one used by Frith in terms of error monitoring requirements but the presentation of the tasks were very different. Frith and Done's study included a game format with a gunman required to shoot birds using a joystick. Further differences stemmed from the fact that affective psychotic participants were included in Frith's study and delusions were not rated just noted as present based on medical notes.

8.5.1 Conclusion

FTD performance could not be assessed due to low levels of the symptom and a skewed distribution. An examination of the delusion results showed that there was no relationship between delusions and cognition. It was difficult to compare the current study to earlier studies due to methodological differences. Future studies should consider collecting more participant information to determine if there is a relationship between delusions and cognition that is mediated by other factors such as motivation, anxiety etc.

CHAPTER 9: CONCLUSIONS

DECLARATION FOR THESIS CHAPTER 9

Declaration by candidate:

In the case of Chapter 9, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution
Selection of behavioural tasks, data collection, data analysis and writing of the chapter.	90%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Susan Rossell	Supervisor of Erica Neill's PhD. Provided assistance in data analysis and proof reading of the chapter

Candidates Signature: [redacted] **Date: 14/01/13**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the Monash Alfred Psychiatry Research Centre and will be held for at least five years from 2009

Susan Rossell [redacted] **Signature:** **Date: 14/01/13**

The aim of this thesis was to better understand the cognitive deficits associated with schizophrenia. This is a worthy avenue of investigation as pharmacological and psychological therapies are limited in the treatment of schizophrenia (Dickerson, 2000; Lieberman et al., 2005). Partly, it seems, because of their failure to ameliorate the cognitive deficits associated with this illness (Meltzer et al., 1999; Rector & Beck, 2001). A greater understanding of the cognitive deficits associated with schizophrenia will provide data which will inform the development of cognitive remediation programs to add to our battery of treatment choices for this group.

The literature has shown that schizophrenia is associated with deficits in almost all areas of cognition (Heinrichs & Zakzanis, 1998; Meltzer & McGurk, 1999). There is some suggestion however, that executive function and memory are particularly impaired and further, predictive of functional outcome (Green et al., 2000). Given the significance of deficits in these areas, they were chosen as the focus for the current thesis. The following paragraphs reiterate the reasons for the lines of inquiry made, and provide a summary of the executive function and semantic memory study results found. The final paragraph suggests future research directions based on the findings of the thesis.

Although, a great deal of this thesis was spent examining the relationship between semantic and executive deficits and the specific positive symptoms of sz (TD and delusions) the current data did not reveal any definitive conclusions regarding these relationships. This symptom discussion was presented in Chapter Eight and will not be reiterated further here.

9.1 Executive Function Conclusions

It has been estimated that between 40-95% of individuals with schizophrenia have significant impairment in executive functioning (Velligan & Bow-Thomas, 1999). This impairment has been linked to outcome generally (Green et al., 2000; Martinez-Aran et al., 2002), and with work function and activities of daily living specifically (Velligan, Bow-Thomas, Mahurin, Miller, & Halgunseth, 2000). Cognitive remediation studies targeting executive functioning have noted some improvements, although these have been limited (Wykes et al., 1999). One of the impediments to developing more effective remediation programs may stem from the fact that we still have a poor understanding of the nature of executive deficits in schizophrenia. At this stage, there is no literature specifically investigating whether executive deficits reflect a specific problem in higher level thinking or whether this dysfunction is, in fact, the result of deficits in lower order processes which then create a difficulty in performing normally on measures of higher level thinking. There is very little data exploring this area in schizophrenia despite the fact that the wide ranging cognitive deficits in this group indicates that this is an obvious area of consideration. One study that examined this issue directly found that executive deficits in this group can, in some cases, be attributed to slowed processing speed (Savla et al., 2010). It was therefore an aim of this thesis to investigate whether lower order deficits do in fact determine executive functioning.

9.1.1 Exploring the influences of executive function on semantic fluency

As a subsection of this investigation, a commonly used semantic task, the semantic fluency task, was investigated in Chapter Six. This task is heavily relied upon to make conclusions about the integrity of semantic function in schizophrenia (Bokat & Goldberg, 2003; Henry & Crawford, 2005). There is evidence however, that this task is confounded by its mutual reliance on executive skills.

Therefore, in the spirit of understanding the relationship between executive functions and other cognitive skills, an investigation was included examining the role of executive function in semantic fluency. This chapter is currently under review for publication with Cognitive Neuropsychiatry.

Traditional studies examining semantic fluency performance in schizophrenia include the semantic and phonemic fluency tasks (Doughty & Done, 2009). The phonemic task is often included as an executive task. If greater impairment is found on the semantic versus phonemic task, this is seen as evidence that semantic function specifically is impaired. The study included in the current thesis improved on previous literature by matching the semantic and phonemic fluency tasks on discriminating power (Melinder et al., 2005), something that has not been done previously. Matching the two fluency tasks on discriminating power ensures that group differences across the tasks can safely be attributed to the underlying cognitive areas of interest rather than to differences in task difficulty. In addition to improving on previous task choice, the current study included another fluency task that requires both semantic and executive skills to complete. It was proposed that if impairments on this task remained after executive influences were controlled for, this would provide additional support for the proposal that the poor semantic fluency performance, often found in schizophrenia, is driven by semantic specific impairments. The results of this study provided support for the fact that semantic fluency performance is driven by semantic impairment when the two traditional tasks were compared in a schizophrenia group. Further, on the additional task, ANCOVA analysis showed that it was a semantic deficit driving performance, even on a task which required additional executive skills, further bolstering the findings of the traditional comparison between phonemic and semantic fluency. Therefore, this thesis supports the use of the semantic fluency task as a measure of semantic function in

schizophrenia. The benefit of being able to use this task is that it is very quick to administer whilst still providing important information about semantic function.

9.1.2 Exploring the influences of lower order cognition on executive function

In Chapter Seven, the contribution of lower order skills to performance on two well-known measures of executive function was investigated. This chapter is currently under review for publication by Schizophrenia Research. The two executive tasks, the Stroop and the Trails task, were selected from the Delis Kaplan Executive Function System (D-KEFS). The D-KEFS was designed to divide out the contributions of lower order cognitive skills (such as processing speed and attention) from performance on executive function measures. The results showed that when reaction time performance was broken down, impairment on the tasks in the schizophrenia cohort was due to non-executive skills. On the Stroop task, reading speed was responsible for group differences; and on the Trails task, differences stemmed from slowing in motor speed and visual scanning. The error data on the other hand, painted a different picture. It appears that on the most difficult components of each task, errors were indicative of an executive problem (not confounded with lower processing skills). Many studies of schizophrenia relying on these two tasks report only on reaction time data. The message of this chapter is that error data may provide a better variable for understanding executive deficits when using these two tasks.

9.2 Semantic Memory Conclusions

The following summary regarding semantic function in schizophrenia will begin with a justification for the area of interest. This will be followed by an examination of analogue studies exploring semantic function, then the schizophrenia study using the same tasks and finally, a paragraph

which compares the analogue to schizophrenia results. Finally, some general conclusions about semantic function in psychosis will be presented.

With regards to memory function, there is already a large, well established literature concerned with episodic memory deficits in this group (Rushe et al., 1999). Further, cognitive strategies for dealing with episodic deficits are already available (Dickinson et al., 2009). Semantic memory has also been investigated in schizophrenia; however, this research has been mostly limited to priming studies (Pomarol-Clotet et al., 2008), and examinations using language tasks designed for use in aphasia or dementia groups (McKay et al., 1996). Currently, there is very little research available examining the differences in implicit and explicit semantic function in schizophrenia. For example, while there is some evidence for deficits in each area, no one study has actually compared implicit and explicit access in the same study sample. As such, one chapter of this thesis was concerned with investigating implicit and explicit semantic function in a schizophrenia group. As a subsidiary to the main aim of examining implicit and explicit semantic function, analogue models of semantic deficits across implicit and explicit memory were also investigated. The following summary of results will first describe the performance of the analogue models, this will be followed by a summary of the schizophrenia group results and finally, analogue and schizophrenia performance will be directly compared on the same tasks – a comparison that ha never been made before.

9.2.1 Analogue models of semantic function in schizophrenia

The purpose of including the analogue models was to evaluate their ability to mimic the semantic deficits and psychotic symptoms associated with schizophrenia. It was determined that this was a valuable addition to this thesis as the number of publications now relying on analogue models to

make comment on the semantic deficits in schizophrenia is growing. Particularly those studies using the ketamine (Adler et al., 1998; Curran & Morgan, 2000; Morgan et al., 2004; Morgan et al., 2004) and the schizotypy analogue models (Johnston et al., 2008; Morgan, Bedford, et al., 2006; Moritz, Andresen, Naber, et al., 1999; Niznikiewicz et al., 2002; Pizzagalli et al., 2001). It is time, therefore, that the validity of these models in mimicking semantic deficits was assessed.

The ketamine model of psychosis is a part of a larger glutamate model. It proposes that schizophrenia is related to abnormalities in the glutamate system (Javitt, 2007). This model is complimentary to the dopamine model of schizophrenia but there is some evidence to suggest that it may be better in mimicking schizophrenia deficits than dopamine agonist drugs (Coyle, 1996). While amphetamines are capable of eliciting positive symptoms, ketamine is able to mimic aspects of positive, negative and cognitive symptoms associated with schizophrenia. There is now a sizable literature using ketamine to model the semantic memory deficits seen in schizophrenia (Adler et al., 1998; Curran & Morgan, 2000; Morgan et al., 2004; Morgan et al., 2004). These studies have provided results suggesting that ketamine can accurately mimic aspects of the semantic dysfunction seen in this disorder. The current thesis compared implicit and explicit semantic function after the administration of ketamine, an approach which has never been taken before. This paper was published in Journal of Clinical Psychopharmacology an is included as Appendix B (Neill et al., 2011). The results of this study showed that when healthy participants were under the influence of ketamine, their performance mimicked one of the few well replicated priming findings from the schizophrenia literature; specifically, they demonstrated hyperpriming in response to indirect stimuli (Minzenberg et al., 2002; Pomarol-Clotet et al., 2008). In terms of implicit versus explicit performance, implicitly, there were reaction time abnormalities whilst explicitly; there were error differences between conditions.

Implicitly, ketamine led to abnormal reaction time priming with greater indirect priming after ketamine administration (there was an error difference between conditions but given the low level of errors made on this task, this finding is not considered meaningful). This finding of enhanced indirect priming supports one of the few reasonably consistent findings in the schizophrenia literature (Rossell & Stefanovic, 2007). Explicitly, ketamine led to more errors on the indirect task across related and unrelated pairs suggesting a difficulty with strategic processing for distantly related pairs.

The schizotypy analogue is based on the proposition that psychosis is on a continuum from a healthy mental state to severe psychosis (Claridge, 1997). Therefore, healthy participants high on measures of schizotypy are thought to provide a good intermediate measure of psychotic and cognitive symptoms associated with schizophrenia. Whilst also controlling for the confounding effects of medication and negative lifestyle effects that are associated with long term mental illness (Claridge, 1994). Based on the finding that schizotypy can mimic cognitive deficits, there is now a large body of literature examining semantic function in this group (Johnston et al., 2008; Morgan, Bedford, et al., 2006; Moritz, Andresen, Naber, et al., 1999; Niznikiewicz et al., 2002; Pizzagalli et al., 2001). Once again, while these studies demonstrate some ability to mimic schizophrenia semantic dysfunction, none of them have examined implicit and explicit semantic access in this group. In the current thesis, implicit and explicit semantic access was explored. The results showed that the high schizotypy group performance mimicked some aspects of schizophrenia performance, that is, they demonstrated more errors on the implicit indirect task than a low schizotypy group. The results of this study must be interpreted with caution however, as the low schizotypy group did not perform the way a healthy control group would be expected to perform suggesting they were not an appropriate comparison group. This chapter is currently being reviewed for publication by Cognitive Neuropsychiatry.

9.2.2 Analogue models compared to schizophrenia performance

In Chapter Four, the schizophrenia study using these semantic tasks found intact implicit and impaired explicit performance in terms of general reaction time, supporting more general memory findings in schizophrenia (Bazin & Perruchet, 1996). The most novel finding of the chapter was that semantic priming performance demonstrated the opposite pattern; characterised by impaired implicit and intact explicit performance. This chapter is currently in press with Psychiatry Research and is included as Appendix D.

Chapter Five consisted of a direct comparison of the analogue groups to the schizophrenia group examined in Chapter Four. These results showed that the schizotypy analogue does appear to successfully demonstrate milder versions of schizophrenia semantic deficits. The ketamine analogue on the other hand, provides a useful model from which to examine impairments in semantic access. It does not provide a full model of schizophrenia semantic deficits however, as the drug is not able to mimic the storage memory deficits associated with this disorder. Therefore, future research interested in looking at schizophrenia specific semantic deficits would be better to use the schizotypy analogue whilst those interested in testing models of semantic function (the access/storage deficit) would be wise to use the ketamine model.

The final conclusions of this thesis can be summarised thusly: (1) The semantic fluency task is an appropriate measure of semantic memory function in schizophrenia. Further, future studies should match the phonemic and semantic fluency tasks on discriminant validity to ensure that differences in cognitive skills are being examined rather than differences in task difficulty. (2) When using the Stroop

and Trails tasks to measure executive function, error data should be examined over reaction time data. Further, future studies should consider the effects of lower order skills on all measures of executive function. (3) In schizophrenia, implicit reaction time performance was intact whilst explicit reaction time and error data performance was impaired. This finding supports general episodic findings in schizophrenia. The priming results however, represent a special case. In terms of priming, implicit performance was impaired whilst explicit performance was impaired. This combination of findings is new in the schizophrenia literature. (4) Finally, the schizotypy analogue appears to provide a good model for schizophrenia deficits as the schizotypy group demonstrated similar but milder versions of the semantic impairments elicited by the schizophrenia group. The ketamine analogue on the other hand, provides a model for access deficits but is not able to mimic schizophrenia deficits specifically.

It is difficult to relate all the findings from this thesis to the development of cognitive remediation programs. There are a couple of specific findings, however, which can be directly considered in the creation of such programs. Firstly, the finding that executive dysfunction may stem from impairments in lower order cognitive skills is an important one. It would be difficult to design a program to remediate executive deficits if lower order influences were not considered. The current results suggest that lower level deficits must be remediated/compensated for first before executive function can be improved. Further, the finding that the semantic fluency task is an appropriate measure of semantic function may also be helpful. Given the variation in schizophrenia cognitive performance, it seems obvious that screening of an individual's specific problems should be undertaken prior to the initiation of remediation to determine the areas of greatest deficit so they can be targeted. The semantic fluency task would seem a good candidate for inclusion in such a screening battery given the speed of administration of this task and the wealth of information it provides (total output, errors analysis and

cluster analysis). The implicit/explicit findings cannot be so easily related to remediation strategies at this point. The finding that implicit and explicit reaction time and error data provide a different pattern of function than priming data needs further exploration. At this point however, this result is important as it suggests that literature regarding reaction time/errors should be considered separately from priming results in informing remediation possibilities.

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APPENDICES

APPENDIX A: Review of Semantic Priming Tasks

An evaluation of explicit semantic tasks to assess their suitability for use in the current thesis

Starting with the Peabody test, this test was quickly disregarded as it is a naming task and does not require any comprehension of relationships between semantic items. The format of this task was therefore considered to be too different to the implicit priming tasks.

The Boston Naming Task includes items of high and low frequency which was not a primary consideration of this thesis. Although it would have been valuable to examine this, trying to create a direct and indirect task and include another task to examine frequency effects would have made the test battery too long and may have confounded results. Trying to combine frequency into the direct and indirect tasks would have been too difficult given the number of lists that needed to be created so this option was rejected (see Chapter Two for details of the implicit priming tasks). The next problem with the Boston is that it is a visual task only. It was decided that the implicit priming tasks would be presented in a written format as this was in line with the indirect findings and is the more commonly used method for presenting priming tasks. By using the common method, it is more comparable to the existing literature. It was therefore decided that the Boston Naming Task would not be used.

The Pyramids and Palm Trees test includes both a visual and a written format making it more compatible with the implicit task. It was disregarded as an option however, as it requires

participants to select from multiple stimuli which is a very different format to the implicit priming format (the Camels and Cactus test was disregarded for the same reason).

Appendices