Semantic priming, schizophrenia and the ketamine model of psychosis

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This thesis is submitted for the degree of Doctor of Philosophy

University College London

November 2009

Declaration

I, Ana Stefanović, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

The central aim of the studies presented in my thesis was to investigate the modulation of semantic memory function and its neural correlates in relation to schizophrenia. Semantic information is stored information that is impersonal, and includes knowledge of words and their meaning, and general knowledge about the world. Semantic memory deficits are thought to underlie core symptoms of schizophrenia, including delusions, thought disorder and alogia. The semantic priming (SP) paradigm has been used extensively to assess semantic memory function. In SP experiments, healthy individuals usually respond faster to target words (e.g. *atlas*) when these are preceded by semantically related prime words (e.g. *map*) than when preceded by unrelated prime words (e.g. *chess*)—referred to as the SP effect. My thesis combined several approaches, using SP as the main tool. First, a behavioural study was conducted with patients with schizophrenia. Second, two neuroimaging experiments investigated modulation of neural correlates of SP in schizophrenia. Last, two studies utilised the ketamine model of psychosis in healthy volunteers to investigate: *(i)* the effects of acute ketamine administration on semantic memory function in drug-naïve participants, and *(ii)* the effects of repeated ketamine administration, seen in those who use ketamine recreationally.

In summary, three key findings indicate that the employment of conscious strategies during semantic processing is impaired *(i)* by acute ketamine administration to healthy volunteers, and *(ii)* in schizophrenia patients as indicated firstly by behavioural results, and *(iii)* secondly by altered prefrontal haemodynamic activation. None of my studies found any modulation of SP when strategic influences were limited i.e. under automatic conditions. My findings suggest that the disrupted semantic processing in schizophrenia is associated with the modulation of the so-called 'executive functions' and prefrontal haemodynamic responses. Future research should explore whether or not this impairment is specific to semantic memory processing.

Acknowledgments

I would like to sincerely thank Prof. H. Valerie Curran for being an amazing supervisor and a great role model—I feel honoured to have been given the opportunity to work with, and learn from her. I am eternally grateful to my family who supported me in so many ways during my PhD, I could not have done it without them. I am also very grateful to Dr. Susan L. Rossell, Dr. Celia J. A. Morgan, Dr. Jonathan P. Roiser, and Dr. Oliver J. Mason, for their guidance and advice. Finally, I would like to thank everyone who participated in my studies and helped with data collection, and Eugene Wahrlich for proofreading my thesis.

Publications

Work included in this thesis has also been published in the following articles:

Stefanovic, A., Roiser, J. P., Joshua, N. R., Neill, E., O'Regan, A., Morgan, C. J. A., Curran, H. V. & Rossell, S. L. (submitted) Modulated prefrontal neural response during a semantic priming task is associated with delusions in schizophrenia.

Stefanovic, A., Brandner, B., Klaassen, E., Cregg, R., Nagaratnam, M., Bromley, L., Das, R. K., Rossell, S. L., Morgan, C. J. A. & Curran, H. V. (2009) Acute and chronic effects of ketamine on semantic priming: modeling schizophrenia? *Journal of Clinical Psychopharmacology*, 29(2), 124-133.

Freeman T. P., Morgan, C. J. A., Klaassen, E., Das, R. K., **Stefanovic, A.**, Brandner, B. & Curran, H. V. (2009) Superstitious conditioning as a model of delusion formation following chronic but not acute ketamine in humans. *Psychopharmacology (Berl)* [Epub ahead of print]

Mason, O. J., Morgan, C. J. A., **Stefanovic, A.** & Curran, H. V. (2008) The Psychotomimetic States Inventory (PSI): Measuring psychotic-type experiences from ketamine and cannabis. *Schizophrenia Research*, 103, 138-42.

Rossell, S. L. & **Stefanovic, A.** (2007) Semantic priming effects in schizophrenia. *Current Psychiatry Reviews*, 3, 137-145.

Table of contents

List of figures

List of tables

Selected abbreviations and acronyms

2-AFC	Two-alternative forced choice
BOLD	Blood-oxygen-level-dependent
BPRS	Brief Psychiatric Rating Scale
EEG	Electroencephalography
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
LD	Lexical decision
LPC	Late positive component
NMDA	N-methyl-D-aspartate
O-LIFE	Oxford-Liverpool Inventory of Feelings and Experiences
PANSS	Positive and Negative Syndrome Scale
RMANOVA	Repeated measures analyses of variance
ROI	Region of interest
RT	Response time
SD	Standard deviation
SOA	Stimulus onset asynchrony
SP	Semantic priming
WP	Word pronunciation

Chapter 1: Introduction

> *Nothing is more common than the idea that we, the people living in the Western world of the twentieth century, are eminently sane…We are sure that by introducing better methods of mental hygiene we shall improve* still further *the state of our mental health, and as far as individual mental disturbances are concerned, we look at them as strictly individual incidents, perhaps with some amazement that so many of these incidents should occur in a culture which is supposedly so sane.*
>
> Erich Fromm (1955, pp. 3)

Schizophrenia is estimated to affect less than 1% of world's population in their lifetime (Saha et al., 2005). Due to the severity of symptoms and the impact it has on a person's life, schizophrenia is rated among the top 10 causes of disability in the world by the World Health Organisation (2001). Although some progress has been made in the treatment of schizophrenia, the underlying pathology is ever so elusive. Eugen Bleuler coined the term "schizophrenia" (Greek: *schizo* - split; *phrene* - mind) at the beginning of the 20th century (Bleuler, 1950), to suggest that at the core of the illness, there is a separation between different mental functions. Perhaps the most pragmatic definition today is that schizophrenia is a group of disorders with similar and overlapping clinical manifestations (for a review see Tandon et al., 2009), including positive and negative symptoms and cognitive dysfunction (for an alternative view see Andreasen et al., 1999). In other words, it is a multidimensional construct (Steel et al., 2007).

Since the times of Bleuler, loose, mediated and oblique associations in thought have been regarded by some as the major contribution to the schizophrenia phenomenology (Neuchterlein & Dawson, 1984). In recent years, investigators have addressed such 'association' disturbances in schizophrenia patients with a growing literature focused upon semantic deficits (e.g. Chen et al., 1994; Goldberg

& Weinberger, 2000; McKenna et al., 1990; Rossell et al., 1998; Rossell & David, 2006). Semantic information is stored information that is impersonal, and includes knowledge of words and their meanings, knowledge of objects and their interrelationships, and general knowledge about the world (Schacter et al., 2000). Semantic deficits are predicted to underlie disturbances in thought and language in schizophrenia, which might not only explain the deficits observed in other cognitive domains, but also provide a cognitive explanation for some core symptoms of schizophrenia, such as, delusions (Rossell et al., 1999), thought disorder (Gouzoulis-Mayfrank et al., 2003; Kerns & Berenbaum, 2002; Spitzer, 1997) and alogia (Sumiyoshi et al., 2005). This thesis takes several different approaches to investigate semantic memory disturbances in relation to schizophrenia symptoms.

One popular experimental technique used in semantic memory research is *semantic priming* (SP). In SP experiments, healthy individuals usually respond faster to target words (e.g. *pear*) when these are preceded by semantically related prime words (e.g. *apple*) than when preceded by unrelated prime words (e.g. *brick*). SP has been used extensively to implicitly assess semantic memory function and is also the main tool in my investigation. This chapter begins with a theoretical background of SP research (section 1.1), including the main theories that have been developed to interpret the SP effect. This is followed by a literature review of SP studies in schizophrenia (section 1.2), and a review of studies on pharmacological manipulations of SP (section 1.3).

Studies investigating modulation of normal function in schizophrenia have repeatedly yielded inconsistent results in many areas of cognitive research (Henry & Crawford, 2005; Lee & Park, 2005). One of the possible reasons for this discrepancy is the high variability in patients' symptom profiles between studies. There is significant heterogeneity in clinical profiles, as well as in the course of schizophrenia and the response to treatment across patients. For this reason, 'schizophrenia' should not be considered a single diagnostic category (Heinrichs,

2004); some of the research on schizophrenia has focused on defining biologically meaningful 'schizophrenia subtypes' (e.g. Heinrichs, 2004; Jablensky, 2006). Alternatively, one could adopt a *'symptoms-orientated approach'* (Bentall, 2003) by investigating cognitive or neurobiological changes in relation to particular symptoms instead of treating schizophrenia as a homogenous entity.

An additional difficulty in schizophrenia research is that results could be affected by secondary changes associated with schizophrenia (e.g. hospitalisation, prolonged use of antipsychotic medication, and possible decline in intellectual functioning) and not as a direct effect of underlying pathology. Some studies have attempted to circumvent this by employing pharmacological models of schizophrenia, inducing transient changes in healthy volunteers (Angwin et al., 2004; Copland et al., 2003a; Copland et al., 2009; Gouzoulis-Mayfrank et al., 1998; Kischka et al., 1996; Morgan et al., 2006b; Roesch-Ely et al., 2006; Spitzer et al., 1996).

Considering the confounds associated with schizophrenia research described above, I used two key approaches:

1. Investigating the modulation of SP in schizophrenia patients (chapters 4, 5 and 6).
2. Utilising the ketamine model of schizophrenia in healthy volunteers (chapters 2 and 3).

Chapter 2 looks at semantic memory disturbances induced by acute ketamine administration in healthy volunteers. This is followed by an investigation of semantic memory changes in people who repeatedly use ketamine recreationally, thus providing a window into the effects of chronic ketamine administration (chapter 3). Chapter 4 is a brief report on a behavioural study conducted with patients with schizophrenia, while chapters 5 and 6 expand on this by providing neuroimaging data on SP in schizophrenia. The final chapter is a synthesis and a

discussion of my results in relation to previous research, and an evaluation of the SP paradigm as a research tool (chapter 7).

1.1 What is semantic priming?

It all started almost four decades ago, when Meyer and Schvaneveldt (1971) simultaneously presented two sets of strings to 12 students, asking them to press a 'yes' key if both sets of strings were real words, or alternatively, to press 'no' if they were not (lexical decision, LD). In half of the real word pairs, the words were associatively related (e.g. *nurse* - *doctor*), and in the other half they were unrelated (e.g. *bread* - *doctor*). Response times (RTs) to related word pairs were on average 117 ms shorter than to unrelated pairs. Accuracy was also significantly higher for related pairs.

This RT and accuracy advantage for related word pairs is now known as SP. SP typically refers to priming occurring due to semantic (e.g. *cat* - *dog*) and/or associative (e.g. *lock* - *key*) relations. Paradigms utilising the SP phenomenon as a tool to investigate semantic memory have become very popular; as of May 2009, there have been over a 1,000 articles published on SP (ISI Web of Knowledge). A typical SP task is presented in Figure 1.1.

In addition to the LD task used in the initial study, SP has been found using a variety of tasks. For instance, in a word pronunciation (WP) task when target words are read aloud (Kwapil et al., 1990; Vinogradov et al., 1992), and also in categorisation tasks (Raposo et al., 2006). More recently, a two-alternative forced-choice paradigm (2-AFC) has been employed to investigate the SP effect (Huber et al., 2001; Quelen et al., 2005).

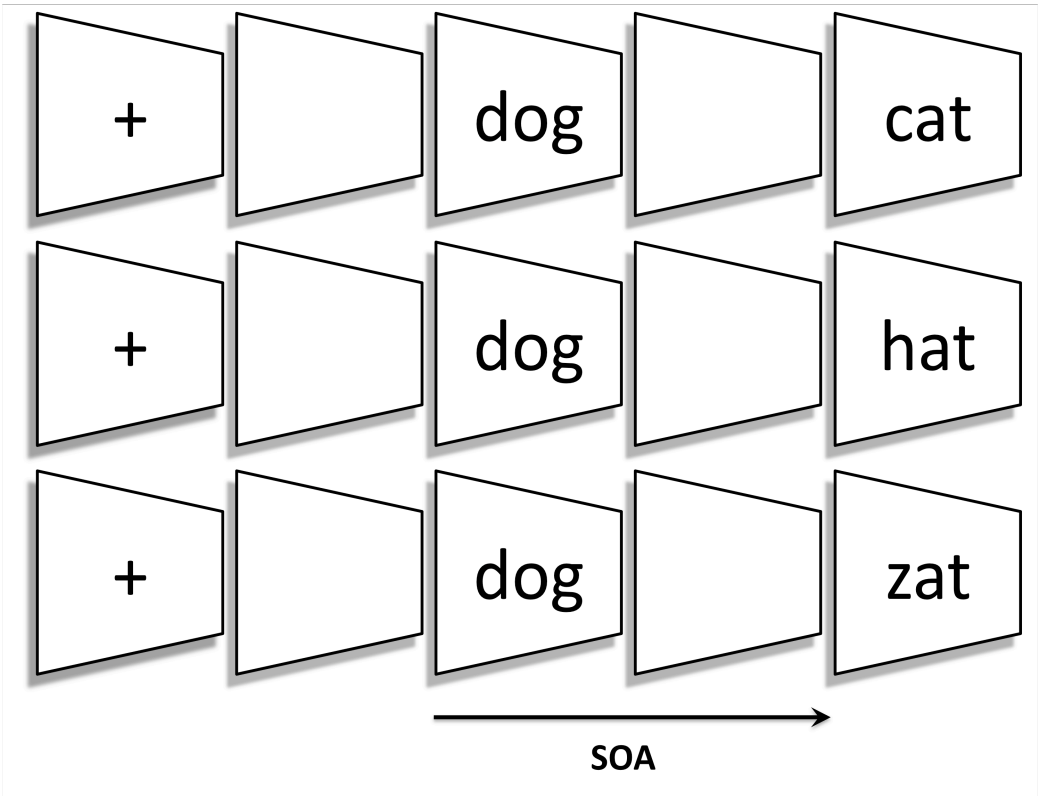


Figure 1.1 Semantic priming lexical decision task

A fixation cross is presented on the screen, followed by a blank screen and then the prime word (*dog*). After a delay, the target word is presented that can either be semantically related to the prime (*cat*), unrelated (*hat*) or a non-word (*zat*). The participant has to decide whether the target is a real word or not. **SOA** – stimulus onset asynchrony is the time elapsed from the onset of the prime to the onset of the target, including any delay between them.

The main theories that have been proposed to explain the SP effect include:

(i) The *automatic spreading activation model* (e.g. Collins & Loftus, 1975; Posner & Snyder, 1975) is based on Quillian's (1967) model of memory. In this model, concepts in memory are represented by localist 'nodes', which are interconnected by links (Figure 1.2). The links correspond to various types of relations between these concepts. Words that are connected

directly and/or through many pathways (e.g. *pear* - *apple*) are more similar in meaning. When a concept is retrieved from the memory, for example by reading the word *pear*, its internal representation—the node—is activated. Furthermore, activation spreads from this node to associated concepts (e.g. *apple*, *fruit*, *tree*).

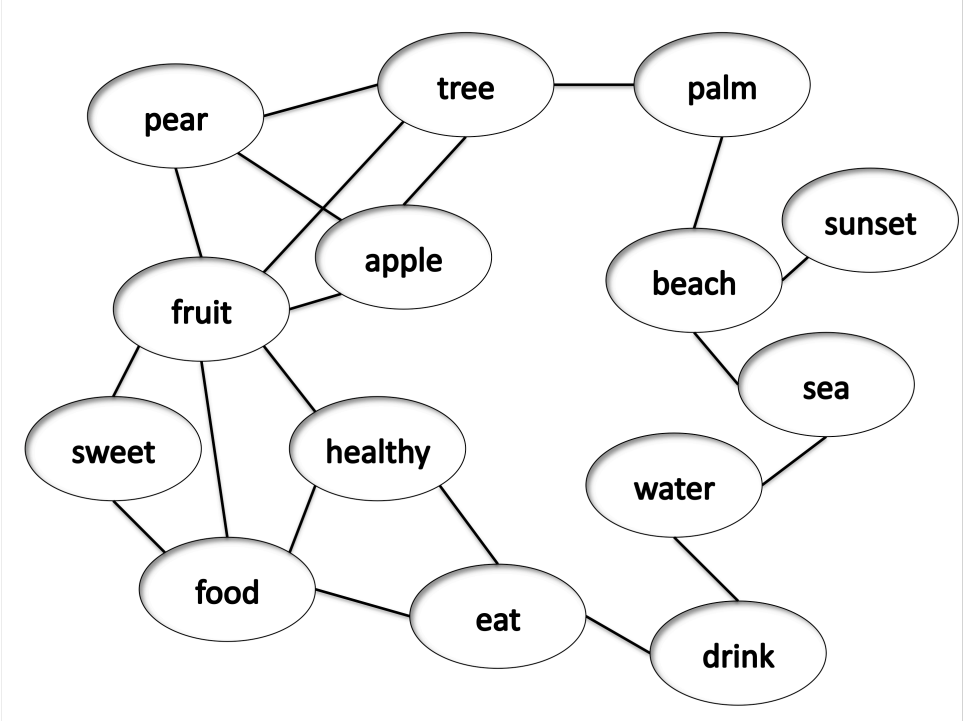


Figure 1.2 A schematic representation of a fragment of the semantic memory network

In the SP task, the presentation of a prime word pre-activates the related target word and this facilitates the subsequent retrieval of the target; there is no facilitation for unrelated targets. This results in faster RTs to related word pairs than to unrelated pairs, and thus to SP. As the activation spreads through the semantic network, it also pre-activates concepts that the prime is 'indirectly' related to, that is, through mediating concepts. For example the words *beach* and *water* are related through the mediating word *sea* (Figure 1.2); reading the word *beach* facilitates the processing of the word *water*. SP obtained through mediation is referred to as *indirect* SP.

Indirect SP is often employed to index the rate of spreading of activation between the hypothetical nodes. It is especially popular in schizophrenia research, where 'disorganised' speech is argued to result from abnormal spreading of activation (section 1.2). The spreading of activation is considered to be the canonical model of SP, and the majority of SP studies interpret their findings within its framework.

(ii) The *compound cue model* (Dosher & Rosedale, 1989; Ratcliff & McKoon, 1988), in contrast to the spreading of activation model, emphasises short-term memory processing. The prime and the target words presented in a pair are thought to join together forming a *compound cue* in the short-term memory. These compound cues are thought to have different degrees of 'familiarity'. Compound cue theory has been discussed within various models of memory, however, regardless of the framework in which it is considered, familiarity refers to the strengths of associations between the compound formed by the prime-target pair in short-term memory and the items in long-term memory.

For instance, in the *search of associative memory model* (SAM; Gillund & Shiffrin, 1984), the items in the long-term memory are referred to as images. All items in the short-term memory are associated to some degree with images in the long-term memory, including novel non-words. However, the strongest associative strength is between a cue and its own image. In this model, familiarity is inversely related to RTs (Ratcliff & McKoon, 1988). Considering that the familiarity of a cue containing related words is higher than familiarity for unrelated words, the RT to the former will be shorter, thus accounting for basic SP effects.

(iii) The *distributed network memory model* (McClelland & Rumelhart, 1985) represents concepts with patterns of activation across a network of interconnected units. Units, which represent different aspects of a concept,

are organised into modules, for example, visual, verbal, and semantic representation modules (Farah & McClelland, 1991). In addition to connections between units in the same module, there are connections between units in different modules, for example the verbal module and the semantic representation module. The specific pattern that is activated by reading a particular word, or thinking about it, is determined by the weights on the connections between the units. In this model, knowledge is encoded in the weights. The progressive feature of this memory model is its plasticity: it can be trained to produce appropriate output from the semantic representation module, such as a meaning of a word, in response to the orthographic properties of a word which is being read. In other words, it can learn.

In a SP task, when a target word is presented its processing starts from the pattern activated by the prime word. The higher the similarity between the prime word and the target word, the higher the similarity between their patterns of activation. Similar to the spreading of activation model, this serves as a 'head start' if the words are related, and this pre-activation facilitates processing of the target. This, in turn, results in SP.

(iv) *Co-occurrence high-dimensional spatial models* are computational models in which concepts are represented as points in a high-dimensional space. For example, in the *hyperspace analogue to language model* (HAL; Lund & Burgess, 1996a; Lund & Burgess, 1996b), concepts are represented as points in Euclidean space whereby the meaning of a concept is encoded in terms of its relations to other concepts in the space. Semantic similarity between two concepts is represented by the distance between their corresponding points in the hyperspace. In the HAL model the vocabulary is built by tracking lexical co-occurrences within a 10-word moving window that slides across a large corpus of text, creating a n x n matrix of co-occurrence values for any given two items, where n is the number of

items in the vocabulary. This value is a weighted frequency of co-occurrence; the closer the two items are in the moving window, the higher the weights.

The meaning of a word is encoded in a vector, which is a concatenation of the row and the column vectors for its item in the co-occurrence matrix. Related words will have similar meaning vectors because they occur in similar contexts, although they might not co-occur in the moving window. HAL has been shown to predict SP effects (Lund et al., 1995), however it underestimates associative SP (Jones & Mewhort, 2007) and does not account for indirect SP (Livesay & Burgess, 1998).

(v) The *composite holographic lexicon model* (Jones & Mewhort, 2007) is based on the same mathematical principles as light holography. Similar to co-occurrence models, the composite holographic lexicon model takes into account the context in which a word appears; however, it additionally encodes the order in which words co-occur, thus providing additional information about their meaning. This distinguishes different meanings of a word. For instance, a holographic lexical representation of the word *bank* would include its meaning in different contexts such as "He was fishing on the river *bank*" and "Someone robbed the *bank*". The composite holographic lexicon model has been shown to account for pure SP, semantic and associative priming, as well as indirect priming (Jones & Mewhort, 2007).

These models provide theoretical explanations for the SP effect, and some of them successfully predict SP effects when computationally modelled, accounting for behavioural SP data. However, they are abstract and are not clearly defined in terms of neuroanatomy. More recently, an attempt has been made to account for SP effects using a computational model based on cortical networks (Lavigne & Darmon, 2008). Although this model requires further refinement, it is a step closer

to bridging the gap between the behavioural, theoretical and neurophysiological SP data.

While the processes described in these theories are thought to be automatic and to occur outside conscious awareness, conscious strategies employed by participants to aid their performance can also contribute to the SP effect (for a review see Neely et al., 1989). For example, when a prime word is presented, the participant can internally generate a set of related words that might appear as a target. If the target that then appears is a member of the generated expectancy set, it is more rapidly recognised, resulting in facilitation; this strategy is referred to as *expectancy*. Participants can also utilise semantic relationships between the prime and target words; if the two words are related, the target must be a real word. This retrospective strategy is referred to as *semantic matching* (e.g. Neely, 1977). Semantic matching leads to a 'real-word' bias for related pairs and a 'non-word' bias for unrelated pairs; i.e. facilitation and inhibition of the target, respectively.

SP task characteristics are commonly manipulated in order to promote or limit strategic processing, especially two particular characteristics. These are the percentage of related pairs (relatedness proportion) and the time elapsed from the onset of the prime presentation to the onset of the target (stimulus onset asynchrony, SOA; Figure 1.1). Short SOAs (< 300 ms) are thought to limit strategic processing, as there is insufficient time to generate an expectancy set (de Groot, 1984; den Heyer et al., 1983), but also because the ongoing processing of the prime interferes with semantic matching. A high relatedness proportion (> 25%) is thought to promote expectancy as the participant becomes aware of the presence of related pairs and starts generating expectancy sets (de Groot, 1984; den Heyer, 1985; Seidenberg et al., 1984). Participants are also more likely to use semantic matching. In summary, high relatedness proportions and long SOAs are thought to promote strategic processing, while low relatedness proportions and short SOAs are usually thought to limit it.

1.2 Literature review I: semantic priming in schizophrenia

1.2.1 Introduction

Quantitatively different patterns of performance in schizophrenia have been used to suggest impairments in the retrieval of information from semantic memory or differences in the actual structure of semantic memory. Rossell and David's (2006) study indicates that structure or storage differences are the key deficit in schizophrenia, while Doughty et al. (2008) found no evidence of storage degradation but instead suggest that access is impaired.

My review of the literature shows that the results in schizophrenia studies to date have been inconsistent (Table 1.1). Some studies report *increased* SP i.e. greater reduction in RTs to related targets relative to unrelated targets (Baving et al., 2001; Chenery et al., 2004; Gouzoulis-Mayfrank et al., 2003; Henik et al., 1992; Kwapil et al., 1990; Manschreck et al., 1988; Moritz et al., 2001b; Moritz et al., 2001a; Moritz et al., 2002; Rossell & David, 2006; Spitzer et al., 1993a; Spitzer et al., 1993b; Spitzer et al., 1994; Surguladze et al., 2002; Weisbrod et al., 1998). Others have recorded *decreased* SP i.e. increase in RTs to related word targets (Aloia et al., 1998; Barch et al., 1996; Besche et al., 1997; Besche-Richard et al., 2005; Besche-Richard & Passerieux, 2003; Chenery et al., 2004; Condray et al., 1999; Condray et al., 2003; Henik et al., 1992; Kostova et al., 2003b; Ober et al., 1995; Ober et al., 1997; Passerieux et al., 1995; Passerieux et al., 1997; Rossell et al., 2000; Vinogradov et al., 1992). Furthermore, some studies have reported *normal* SP in schizophrenia (Barch et al., 1996; Besche-Richard et al., 2005; Besche-Richard & Passerieux, 2003; Blum & Freides, 1995; Chapin et al., 1989; Chapin et al., 1992; Gouzoulis-Mayfrank et al., 2003; Henik et al., 1992; Koyama et al., 1991; Koyama et al., 1994; Minzenberg et al., 2003; Moritz et al., 2001b; Moritz et al., 2002; Nestor et al., 2006; Ober et al., 1995; Passerieux et al., 1995; Quelen et al., 2005; Rossell et al., 2000; Rossell, 2004; Rossell & David, 2006; Surguladze et al., 2002; Vinogradov et al., 1992).

Table 1.1 Summary of direct and indirect behavioural semantic priming studies in schizophrenia

Study	Short SOA (< 300 ms)			Mid-range SOA (300–500 ms)			Long SOA (> 500 ms)		
	Participants	**SOA/Task/RP**	**Results**	**Participants**	**SOA/Task/RP**	**Results**	**Participants**	**SOA/Task/RP**	**Results**
Manschreck et al (1988)	*12TD 6NT 11HC 9PC*	*250/LD/20*	*TD > HC/NT/PC*						
Chapin et al (1989)	12SZ 12PC 12HC	0/LD/25	SZ = HC/PC						
Kwapil et al (1990)				*21SZ 18B 21HC*	*500/WP/33*	*SZ > HC*			
Chapin et al (1992)	45SZ 15HC	0/LD/25	SZ = HC						
Henik et al (1992)	**22SZ 17HC**	**240/LD/25**	**SZ < HC**				22SZ 17HC	1840/LD/25	SZ = HC
Vinogradov et al (1992): Exp 1	19SZ 22HC	250/WP/16.7	SZ = HC						
Vinogradov et al (1992): Exp 2	**19SZ 20HC**	**250/LD/8.3**	**SZ < HC**						
Spitzer et al (1993b): Exp DP	*32SZ 32HC*	*200/LD/16.7**	*SZ > HC*				*32SZ 32HC*	*700/LD/16.7**	*SZ > HC*
Spitzer et al (1993b): Exp IP	*32SZ 32HC*	*200/LD/16.7**	*SZ > HC*				32SZ 32HC	700/LD/16.7*	SZ = HC
Spitzer et al (1993a): Exp DP	*29TD 21NT 50HC*	*200/LD/16.7**	*TD > HC TD †> NT*				*29TD 21NT 50HC*	*700/LD/16.7**	*TD > HC*

Spitzer et al (1993a): Exp IP	*29TD 21NT 50HC*	*200/LD/16.7**	*TD > HC/NT*				*29TD 21NT 50HC*	*700/LD/16.7**	*TD †> HC*
Koyama et al (1991; 1994)							11SZ 11HC	1500/LD/33	SZ = HC
Spitzer et al (1994)	*36TD 34NT 44HC*	*200/LD/19*	*TD > HC*	*36TD 34NT 44HC*	*400/LD/19*	*TD > HC*	*36TD 34NT 44HC*	*700/LD/19*	*TD > HC*
Blum & Freides (1995)				9TD 9NT 9HC	350/LD§/25	SZ = HC			
Henik et al (1995)	*16SZ 16HC*	*240/LD/33*	*SZ > HC*				*16SZ 16HC*	*1840/LD/33*	*SZ > HC*
Ober et al (1995): Exp 1 & 3	18/17SZ 21/22HC	250/WP/16.7	SZ = HC						
Ober et al (1995): Exp 2	15SZ 21HC	250/LD/8.3	SZ = HC						
Ober et al (1995): Exp 4	**16SZ 22HC**	**250/LD/8.3**	**SZ < HC**						
Passerieux et al (1995): Exp 1	14SZ 11HC	64/LD/16.7	SZ = HC						
Passerieux et al (1995): Exp 2	**17SZ 11HC**	**240/LD/16.7**	**PD < HC** HB = HC						
Barch et al (1996)	75M 25UM 10PC 25HC	200/WP/50	SZ = HC	75M 25UM 25HC	300/WP/50 450/WP/50	SZ = HC SZ = HC	75M 25UM 25HC	700/WP/50 **950/WP/50**	SZ = HC **SZ < HC**
Maher et al (1996)				30SZ	500/LD/20	LOI↑ SP↓			

Besche et al (1997)				**24TD 10NT 14PC 20HSC 20HC**	**500/LD/25**	**TD < HC**			
Ober et al (1997)	**31SZ 20HC**	**260/LD/7.5**	**SZ < HC**				**31SZ 20HC**	**1000/LD/23.1**	**SZ < HC**
Passerieux et al (1997)				**22SZ 11HC**	**500/LD/16.7**	**TD < HC**			
Aloia et al (1998)				**9TD 11NT 21HC**	**Mid/WP¶/63***	**TD < HC**			
Weisbrod et al (1998): Exp DP	*16TD 24NT 38HC*	*250/LD§/16.7**	*TD > HC*						
Weisbrod et al (1998): Exp IP	*16TD 24NT 38HC*	*250/LD§/16.7**	*TD > HC*						
Goldberg et al (2000)							17SZ	Long/WP¶/63*	Medication↑ SP↑
Rossell et al (2000): Exp DP							**26D 16ND 28HC**	**700/LD/25***	**D/ND < HC**
Rossell et al (2000): Exp IP							26D 16ND 28HC	700/LD/12.5*	D/ND = HC
Baving et al (2001)							*17SZ 20HC*	*Long/LD¶/12.5*	*SZ > HC*
Moritz et al (2001b): Exp DP	16TD 28NT 30HC 36PC	200/LD/16.7*	SZ = HC/PC						
Moritz et al (2001b): Exp IP	*16TD 28NT 30HC 36PC*	*200/LD/16.7**	*SZ > PC not HC TD > NT/PC/HC*						

Moritz et al (2001a)	*30TD 15NT 29HC 35PC*	*200/WP/55*	*TD > NT/HC/PC*						
Surguladze et al (2002): Exp I ‡				20SZ 26HC	400/LD/33	SZ = HC			
Surguladze et al (2002): Exp C ‡				*20SZ 26HC*	*400/LD/33*	*SZ > HC*			
Besche-Richard et al. (2003): Exp 1				15TD 15HC	500/LD¶/25	TD = HC			
Besche-Richard et al. (2003): Exp 2				**15TD 15HC**	**500/LD¶/14.9**	**TD < HC**			
Condray et al (1999; 2003)				**37SZ 34HC**	**350/LD/31&63**	**SZ < HC**	**37SZ 34HC**	**950/LD/31&63**	**SZ < HC**
Gouzoulis-Mayfrank et al (2003): Exp DP #							*16TD 17ND 20HC*	*700/LD/16.7**	*T1: TD > NT/HC* T2: TD = NT/HC
Gouzoulis-Mayfrank et al (2003): Exp IP #							16TD 17ND 20HC	700/LD/16.7*	T1/T2: TD = NT/HC
Kostova et al (2003b)				**12SZ 12HC**	**450/LD/16.7**	**SZ < HC**			

Minzenberg et al (2003)	54SZ 20HC	250/LD/14.8	SZ = HC				54SZ 20HC	1000/LD/14.8	SZ = HC
Moritz et al (2002): Exp DP	12TD 20NT 65HC	200/WP/25*	TD = NT/HC						
Moritz et al (2002): Exp IP	*12TD 20NT 65HC*	*200/WP/25**	*TD > NT/HC*						
Chenery et al (2004): low RP	*14SZ 12HC*	*250/LD/20*	*SZ > HC*	**14SZ 12HC**	**500/LD/20**	**SZ < HC**	**14SZ 12HC**	**1000&2000/LD/20**	**SZ < HC**
Chenery et al (2004): high RP	14SZ 12HC	250/LD/37.5	SZ = HC	14SZ 12HC	500/LD/37.5	SZ = HC	**14SZ 12HC**	**1000&2000/LD/ 37.5**	**SZ < HC**
Rossell (2004)							40SZ 40 HC	700/LD/25	SZ = HC
Besche-Richard et al (2005): Exp1	21TD 20HC	0/LD¶/25	TD = HC						
Besche-Richard et al (2005): Exp2	19TD 20HC	0/LD¶/18.7	TD = HC						
Quelen et al (2005): Automatic							20SZ 20HC	617‖/2-AFC/50	SZ = HC *(TD↑ SP↑)*
Quelen et al (2005): Strategic							20SZ 20HC	617‖/2-AFC/50	SZ = HC
Nestor et al. (2006)				14SZ 14HC	575/LD/10	SZ = HC			
Rossell & David (2006): Low word frequency	2 SOAs together: 32SZ 32HC 250&750/LD/25 SZ = HC								

Rossell & David (2006): High word frequency	*2 SOAs together:*	*32SZ 32HC*	*250&750/LD/25*	*SZ > HC*	

Participants: SZ – schizophrenia patients; **D** – SZ with delusions; **ND** – SZ without delusions; **TD** – SZ with thought disorder; **NT** – SZ without thought disorder; **M** – medicated SZ; **UM** – unmedicated SZ; **HB** – hebephrenic SZ; **PD** – paranoid SZ; **B** – bipolar disorder patients; **PC** – psychiatric controls; **HSC** – hospitalised controls; **HC** – healthy controls. **LOI** – length of illness.

Group differences:

Italics – SZ showed increased SP compared with HC.

Bold – SZ showed decreased SP compared with HC.

Normal – There is no difference between SZ and HC groups.

Tasks: LD – lexical decision; **WP** – word pronunciation; **2-AFC** – two-alternative forced choice.

SOA – stimulus onset asynchrony (in ms); **RP** – relatedness proportion (in %).

Some studies included two SP tasks: a direct SP task (**DP**) and an indirect SP (**IP**); all other studies had DP tasks only.

* DP and IP experiments were randomly incorporated into the same set of test stimuli: in Spitzer et al. (1993a; 1993b), Moritz et al. (2001b), Gouzoulis-Mayfrank et al. (2003), and Weisbrod et al. (1998) the overall relatedness proportion was 33%; in Rossell et al. (2000) it was 37.5% and in Moritz et al. (2002) it was 50%. In Aloia et al. (1998) and Goldberg et al. (2000), related pairs were of different degrees of relatedness (high, medium and low), each comprising 21% of all pairs.

† At a trend level.

‡ Surgaladze et al. (2002) employed 2 conditions: an ipsi-modal (**I**) where prime and target were both presented visually and a cross-modal (**C**) condition in which the auditory presentation of the prime was followed by a visually presented target.

§ Task with a lateralised presentation.

|| The LD had to be made at 650-897 ms (see section 1.2.5 for details).

¶ Participants were required to make responses (LD or WP) to both the prime and the target words. In Aloia et al. (1998) and Goldberg et al. (2000) the target was presented 350 ms after the response to the prime was made, while in Baving et al. (2001) the target followed after 800 ms; in Besche-Richard and Passerieux (2003) and Besche-Richard et al. (2005) response was given to both words simultaneously i.e. 'yes' if both are real words, and 'no' if either is not a real word.

Longitudinal study: T1 – within 10 days since the beginning of a remission episode; T2 – stabilised (3-4 month later).

A number of variables have been identified as possible reasons for the discrepancies in the schizophrenia SP literature: type of task used (WP, LD, 2-AFC), SOA, relatedness proportion, type of stimuli used (i.e. different semantic relationships including indirect relationships), whether the stimuli have lateralised presentation, psychometric artefacts, medication, the symptomatology of the patient sample and other illness characteristics.

This review will summarise the behavioural SP results in schizophrenia in relation to these variables, as well as consider whether electrophysiological studies of SP have been informative about schizophrenia. Functional magnetic resonance imaging (fMRI) studies of SP in schizophrenia are reviewed in chapter 5 and are not included here.

1.2.2 Stimulus onset asynchrony

Some authors have argued that the length of the SOA has important implications for whether or not there is increased or decreased SP in schizophrenia (Table 1.1). Generally, it has been assumed that increased SP in schizophrenia occurs at short (< 300 ms) SOAs (Henik et al., 1995; Manschreck et al., 1988; Moritz et al., 2001a; Spitzer et al., 1993a; Spitzer et al., 1993b; Spitzer et al., 1994; Weisbrod et al., 1998). These results are often interpreted within the spreading of activation model (see section 1.1) to mean that that the automatic processes are altered, whereby the spreading of activation is disinhibited (e.g. Spitzer et al., 1994). In other words, the activation spreads to a greater extent within the semantic network in schizophrenia, and this results in increased SP.

An examination of the literature does not reveal such a clear pattern. Three studies (Besche-Richard & Passerieux, 2003; Chapin et al., 1989; Chapin et al., 1992) employed simultaneous presentation of the prime and the target (i.e. 0 ms SOA) and reported that SP in people with schizophrenia is no different from that of healthy controls. Passerieux et al. (1995) reported similar results using a 64 ms SOA. Studies using a 200 ms SOA from one research group have all shown

increased SP in patients with schizophrenia, especially those with thought disorder (Spitzer et al., 1993a; Spitzer et al., 1993b; Spitzer et al., 1994). Moritz and colleagues (2001b; 2001a; 2002) replicated these findings, using Spitzer's stimulus materials and procedures. However, Barch et al. (1996) did not find a group difference using a 200 ms SOA with different stimulus materials.

Many studies have employed a 240-260 ms SOA. Four of these demonstrated normal direct SP in people with schizophrenia (Minzenberg et al., 2003; Ober et al., 1995; Passerieux et al., 1995; Vinogradov et al., 1992), five studies reported a decrease in SP (no facilitation for related word pairs) in schizophrenia (Henik et al., 1992; Ober et al., 1995; Ober et al., 1997; Passerieux et al., 1995; Vinogradov et al., 1992), and three studies showed an increase in SP in schizophrenia patients (Henik et al., 1995; Manschreck et al., 1988; Weisbrod et al., 1998). The pattern of results for mid-range (300-500 ms) SOAs and long (> 500 ms) SOAs is equally opaque (see Table 1.1). In summary, although it is intuitively appealing to suggest that SP deficits in schizophrenia are due to disinhibited spreading of activation with increased SP at short SOAs, the data reported in the literature do not support such a hypothesis.

1.2.3 Relatedness proportion

Vinogradov et al. (1992) argued that different patterns of results in SP studies in schizophrenia are due to differences in the relatedness proportion utilised and not the usage of different SOAs. The relatedness proportion for all studies in this review was calculated as a percentage of the total number of pairs in a task, including the pairs with non-words. It should be noted, however, that some authors (e.g. Minzenberg et al., 2003) consider it as the percentage of word-word pairs, thus not taking into account pairs that include non-words.

As shown in Table 1.1, a general pattern of results emerges based on the percentages used. Employing a LD task with a low percentage of related pairs (≤ 25%), usually results in equivalent or decreased SP in schizophrenia compared

with healthy individuals (Besche et al., 1997; Besche-Richard et al., 2005; Besche-Richard & Passerieux, 2003; Chapin et al., 1989; Chapin et al., 1992; Henik et al., 1992; Minzenberg et al., 2003; Ober et al., 1995; Ober et al., 1997; Passerieux et al., 1995; Rossell, 2004; Vinogradov et al., 1992). Higher percentages of related pairs (> 25%) produce increased SP in schizophrenia compared with healthy individuals (Henik et al., 1995; Moritz et al., 2001b; Moritz et al., 2001a; Spitzer et al., 1993a; Spitzer et al., 1993b; Surguladze et al., 2002; Weisbrod et al., 1998). This distinction appears to be independent of SOA, and in general holds true.

The nineteen studies cited above show a clear relatedness proportion effect, whereas six further studies do not conform to this pattern: three with a low relatedness proportion (Baving et al., 2001; Manschreck et al., 1988; Spitzer et al., 1994) and three with a high relatedness proportion (Condray et al., 1999; Moritz et al., 2001b; Rossell et al., 2000). Condray et al. (1999) used 31% and 63% and Rossell et al. (2000) used 37.5% related prime-target pairs; both studies found decreased or normal SP in schizophrenia. Rossell et al.'s (2000) task was primarily designed to investigate whether different categories of emotion have any impact on SP in schizophrenia. Therefore, additional methodological factors might have interfered with the relatedness proportion effect. Manschreck et al. (1988) used 20% related prime-target pairs and found increased SP in schizophrenia patients with thought disorder. However, the participant groups in that study were very small. Spitzer et al. (1994) employed 19% of related prime-target pairs and found increased SP in patients with thought disorder. This study included rhyming prime-target pairs. If the rhyming pairs are considered as related, the relatedness proportion is high (30.6%) and their results would therefore be representative of the standard pattern of results.

Baving et al. (2001) used 12.5% related prime-target pairs and showed increased SP in schizophrenia. They used a slightly unusual task procedure, which required participants to make LDs to both the prime and the target words, referred to as 'double LD'. It is unlikely that this methodological difference contributed to their

results as other studies using the double LD paradigm fit the general pattern. For instance, Besche-Richard and Passerieux (2003) and Besche-Richard et al. (2005) used low relatedness proportions in double LD tasks and showed decreased SP or no difference between schizophrenia patients with thought disorder and healthy controls, as expected. Overall, SP is increased in schizophrenia in tasks with a high relatedness proportion and it is decreased or normal in tasks employing low relatedness proportion.

1.2.4 Type of stimuli

An additional factor that might interact with the relatedness proportion effect is the *type* of relatedness between the prime and the target. Moritz et al. (2001a) used homonym prime words. Homonyms are words with one orthographic and phonological code but two or more separate meanings (e.g. *bank*). The target words were semantically related to either the dominant meaning (*money*) or the subordinate meaning (*river*) of the prime. When the target was related to the subordinate meaning of the prime, Moritz et al. reported increased SP in schizophrenia patients with thought disorder compared with three groups: schizophrenia patients without thought disorder, psychiatric controls and healthy controls. They argue that this result provides evidence of decay in hierarchical thinking, i.e. that patients with schizophrenia form associations with the inferior meanings of words. These findings were partially replicated in Moritz et al. (2002) although this study had an extremely small group of schizophrenia patients with thought disorder. Ober et al. (1995) argued that decreased SP in patients with schizophrenia is found in certain circumstances, specifically, in a LD task using prime-target pairs that are horizontally related (i.e. co-members of the same category e.g. *cat* - *dog*), and not vertically related pairs (i.e. superordinate - subordinate relationship e.g. *fruit* - *pear*).

Spitzer and colleagues (1993a; 1993b) published several studies examining indirect SP in schizophrenia, i.e. when the prime and the target are connected via a mediating associated word (e.g. *black* - white - *chalk*). They reported that

schizophrenia patients demonstrate significant indirect SP at both short (200 ms) and long (700 ms) SOAs, whilst healthy controls show indirect SP only at a long SOA. Therefore, schizophrenia patients showed enhanced indirect SP at short and not long SOAs compared with healthy controls. Enhanced indirect SP at a short SOA (Moritz et al., 2001b; Weisbrod et al., 1998) and normal indirect SP at a long SOA (Gouzoulis-Mayfrank et al., 2003) were replicated using the same stimuli and procedures, in schizophrenia patients with thought disorder versus patients without thought disorder and healthy controls. Moritz et al. (2002) also replicated these results at a short SOA using a different relatedness proportion. Spitzer and colleagues interpret the finding that schizophrenia patients with thought disorder exhibit indirect SP at short SOAs, whereas patients without thought disorder and healthy controls do not, as evidence for increased spreading of associational activation in patients with thought disorder.

Rossell et al. (2000) used a 750 ms SOA and did not demonstrate any overall differences in indirect SP between patients with and without delusions, and healthy controls. However, there were group differences when the material was sub-typed into different emotional categories with increased indirect SP using negative valence stimuli. Therefore, group differences using indirect SP methodology at a short SOA are the most replicable to date and potentially the most revealing.

The frequency of occurrence of words presented in a SP task should also be considered. Word frequency is defined as the incidence of a word per one million words in a given language (Kwapil et al., 1990). A word is usually regarded a low frequency word if it has the incidence of 1-30 words per one million. Accordingly, if a word has a greater incidence, it is a high frequency word. Rossell and David (2006) examined words with different frequency in a SP task in schizophrenia, and found increased priming to high frequency stimuli, but not low frequency stimuli, in people with schizophrenia compared with healthy controls. These results have been used as a basis to argue for semantic memory storage deficits in

schizophrenia. They also illustrate the importance of stimuli characteristics. Other stimuli characteristics, including word imageability, concreteness, and ambiguity have as yet received scant research attention.

1.2.5 Type of task

While most researchers have used a LD task, eight studies have employed word pronunciation (WP; Aloia et al., 1998; Barch et al., 1996; Goldberg et al., 2000; Kwapil et al., 1990; Moritz et al., 2001a; Moritz et al., 2002; Ober et al., 1995; Vinogradov et al., 1992). There is no clear relatedness proportion effect when a WP methodology is used. Two studies employing 16.7% of related pairs found normal SP in schizophrenia using WP, similar to the results with an LD task (Ober et al., 1995; Vinogradov et al., 1992). Kwapil et al. (1990) and Moritz el al. (2001a) studies using 33% and 50% of related pairs, respectively, fit the LD pattern in regard to relatedness proportion. In contrast, Barch et al. (1996) used 50% of related pairs and found normal/reduced SP in schizophrenia. In addition, Aloia et al. (1998) used 63% relatedness proportion and found that patients with prominent thought disorder exhibit less SP than healthy participants when the prime-target pairs used are highly associated. The stimuli list in the Aloia et al. study included related pairs of different degrees of relatedness: high, medium and low. If only the percentage of highly related pairs is taken into account, it is a low relatedness proportion study (21%) and thus fits the prediction. An identical paradigm was employed by Goldberg et al. (2000) to investigate the effects of medication on SP (see section 1.2.7).

Ober et al. (1995) compared equivalent WP and LD tasks in the same group of participants, one with horizontally and another with vertically related prime-target pairs (see section 1.2.4). In contrast to the results from the LD tasks, no difference between patients with schizophrenia and healthy controls was found using WP. An earlier study by Vinogradov et al. (1992) also compared a LD and a WP task with identical SOAs in the same group of participants. However, as WP tasks do not contain non-word pairs, the relatedness proportion was lower in the

LD task. They found reduced SP in schizophrenia on the LD task, but no differences between the groups with the WP task. More studies that directly compare LD and WP tasks are required before any final conclusions can be made about how this methodological contrast can influence the results. Unlike LD tasks, there is no semantic matching in the WP task as all targets are real words; however expectancy is still thought to occur.

Quelen et al. (2005) is the only study to have employed the two-alternative forced choice (2-AFC) paradigm in patients with schizophrenia. They argue that this method distinguishes between automatic and strategic influences on SP. In the 2-AFC task, the presentation of the prime and a masked target is followed by the presentation of two words: a target and a foil. The participant has to indicate which one of the two words has been previously presented. The prime can either be semantically related to both the target and the foil, related to just one of them or to neither (relatedness proportion is 50%). Although this paradigm employs longer SOAs, it is designed to investigate both automatic and strategic processes by comparing different conditions (for details see Huber et al., 2001). This study showed no differences between schizophrenia patients and healthy controls at automatic and strategic levels of processing.

An additional manipulation in SP tasks is a lateralised presentation of stimuli. In lateralised tasks, words are presented either to the right or to the left visual field, as opposed to the typical centralised presentation. Words presented to the right visual field are mainly processed by the left hemisphere, and vice versa. In healthy participants, SP studies with lateralised presentation show that RTs to real word targets are faster if the words are presented to the right visual field compared with when they are presented to the left visual field. This effect is referred to as the *right visual field advantage* (Collins & Coney, 1998; Korsnes & Magnussen, 2007), and is though to reflect faster processing in the left hemisphere compared with the right hemisphere. Two studies used lateralised presentation with schizophrenia patients (Table 1.1). Blum and Freides (1995) found normal SP, as

well as the right visual field advantage effect for word targets in schizophrenia patients (with and without thought disorder). This indicates that there is no hemispheric lateralisation deficit in schizophrenia.

Weisbrod et al. (1998) compared direct and indirect SP effects using a lateralised LD task with a short SOA. While there was no difference in direct SP between the hemispheres in either of the groups, the indirect SP task showed a different result. The indirectly related targets were facilitated only in the right hemisphere in healthy participants. In contrast, in participants with schizophrenia the indirect SP effect was obtained in both hemispheres. This result was interpreted as a decreased lateralisation of semantic function in schizophrenia within the SP paradigm. However, the processing of the prime was not limited to one single hemisphere, as it was presented in the centre of the screen. Therefore, replication of these results using a lateral presentation of the prime is required.

1.2.6 Psychometric artefacts

Two major confounds in any RT study that includes schizophrenia patients are the generalised slowing and the more variable RTs compared with healthy individuals. Chapman et al. (1994) reported that slower individuals show a larger difference between related and unrelated word pairs, thus, greater SP. This linear relationship suggests that increased SP in schizophrenia could be the result of a psychometric artefact. Meaningful comparisons between groups can only occur if they are matched on overall performance (e.g. Koyama et al., 1994) or if various statistical treatments are applied after data collection. Many of the SP studies in schizophrenia have not used appropriate statistical techniques (e.g. Besche et al., 1997; Chapin et al., 1989; Chapin et al., 1992; Maher et al., 1996; Manschreck et al., 1988; Ober et al., 1995; Ober et al., 1997; Spitzer et al., 1993b; Vinogradov et al., 1992). In an attempt to circumvent this difficulty, some earlier studies calculated the SP effect based on median RTs instead of mean RTs per condition per participant, suggesting that medians better reflect data in this case (Blum & Freides, 1995; Henik et al., 1992; Henik et al., 1995; Passerieux et al., 1997).

Others have used the regression model proposed by Chapman et al. (1994) to test whether—given the patients' generalised slowing—they show more SP than is expected based on their overall performance (Barch et al., 1996; Baving et al., 2001; Chenery et al., 2004; Moritz et al., 2001b; Moritz et al., 2001a; Moritz et al., 2002). They suggested that the effect of psychomotor slowing on SP should be calculated using a regression equation that is derived from healthy participants' data, preferably from a larger group. This equation is used to compute the predicted SP scores per condition per participant in the slower group. The predicted SP is then compared to the obtained SP by calculating the difference between the two per condition per participant. This indicates whether the participants' SP scores are normal, increased, or decreased, based on what is expected given their overall level of performance. For instance, Moritz et al. (1999) calculated their regression equation based on a large (n = 160) group of healthy participants and used it to compare patients with schizophrenia to healthy participants (Moritz et al., 2001b). Barch et al. (1996) derived the regression equation from a mixture of patients with depression and healthy participants.

In contrast, others have calculated the SP effect as a percentage of either the overall mean RT or mean RT in the unrelated condition in order to take into account patients' slower RTs (Aloia et al., 1998; Baving et al., 2001; Besche-Richard et al., 2005; Besche-Richard & Passerieux, 2003; Goldberg et al., 2000; Gouzoulis-Mayfrank et al., 2003; Nestor et al., 2006; Rossell & David, 2006; Spitzer et al., 1993a; Spitzer et al., 1994; Weisbrod et al., 1998). This method was initially proposed by Spitzer et al. (1993a) who suggested that the way in which the SP effect is calculated can have a major impact on the results obtained. In their study, the significant difference in direct SP between schizophrenia patients with thought disorder and patients without thought disorder and healthy controls was abolished when the SP effect was calculated as a percentage. However, the difference in indirect SP remained.

Although it is not clear which of these methods is most effective, at least one should be employed if one of the groups shows longer RTs and increased SP. For instance, Baving et al. (2001) compared SP effects using both the regression model and the percentage calculation method and found that they produced identical results. Alternatively, the comparison between two groups with expected different mean RTs could be based on accuracy data instead of RTs (Kwapil et al., 1990; Quelen et al., 2005).

1.2.7 Medication effects

Three studies have examined the effects of medication on SP performance in schizophrenia. Spitzer et al. (1994) provided pilot study data on 11 patients during the acute phase of illness at the beginning of treatment and later when medicated, with their symptoms in remission. The results were unclear as to whether the reduction in direct SP and decreased error rates were due to clinical differences or medication. Barch et al. (1996) examined the role of medication more thoroughly, matching medicated and un-medicated patients on positive symptoms. They suggested that increased medication dosage was significantly associated with increased direct SP scores with a SOA of less than 950 ms. Goldberg et al. (2000) established that SP increased with neuroleptic medication, thus approaching normal SP. However, the majority of studies have found no correlation between medication and SP performance (e.g. Gouzoulis-Mayfrank et al., 2003; Moritz et al., 2001b; Moritz et al., 2001a; Quelen et al., 2005; Rossell et al., 2000; Surguladze et al., 2002), or medication and haemodynamic correlates of SP (Kuperberg et al., 2007).

1.2.8 Schizophrenia subtypes and symptomatology

A number of studies have demonstrated that schizophrenia patients with thought disorder show greater increase in direct SP compared with both schizophrenia patients without thought disorder and psychiatric controls (Chenery et al., 2004; Gouzoulis-Mayfrank et al., 2003; Manschreck et al., 1988; Moritz et al., 2001b;

Moritz et al., 2001a; Quelen et al., 2005; Spitzer et al., 1993a; Spitzer et al., 1994; Weisbrod et al., 1998). These interpret their results within the framework of the spreading of activation model (see section 1.1) as evidence that activation within the semantic network is either broader and/or of greater magnitude in thought disorder. However, Aloia et al. (1998), Besche et al. (1997) and Passerieux et al. (1995) demonstrated decreased direct SP in patients with thought disorder compared with patients without thought disorder and healthy controls. Procedural differences are a possible explanation for the discrepancy between these findings.

Rossell et al. (2000) examined the effect of delusions on SP and reported that schizophrenia patients failed to demonstrate significant direct SP, regardless of the presence or absence of delusions; significant direct SP was obtained in healthy controls. When performance was examined according to the emotional valence of the word pairs, neither patient sub-group showed direct SP with positive and negative word pairings; schizophrenia patients with delusions in fact showed a trend toward inhibition of SP with negative stimuli. Controls and non-deluded patients also failed to show direct SP with negative stimuli but did not show inhibition. Indirect SP was obtained in all groups. The main difference between schizophrenia patients with and without delusions was that the former showed less direct SP along with greater indirect SP with the negative material. Rossell et al. propose that delusions may result from strong abnormal indirect associations, in contrast to poorer normal semantic associations toward material of a negative valence. However, as healthy controls showed more indirect priming with the negative word pairs than the patients with delusions, further research is required to support such proposal.

Other studies have also compared schizophrenia subtypes in relation to SP. For instance, Passerieux et al. (1995) examined paranoid and hebephrenic (i.e. predominantly disorganised and negative symptoms) subtypes, diagnosed according to ICD-9. Hebephrenic patients demonstrated the same pattern of

significant direct SP as healthy controls, while the paranoid patients did not show direct SP at a 240 ms SOA. This is supportive of Rossell et al.'s (2000) findings. Chapin et al. (1992) reported no difference in SP in patients with a diagnosis of chronic undifferentiated schizophrenia, paranoid schizophrenia and schizo-affective disorder. Ober et al. (1997) reported no difference between paranoid and non-paranoid subtypes. In summary, there is no clear-cut evidence for a relationship between SP deficits and any symptom of schizophrenia, although thought disorder seems to be often related to increased SP.

1.2.9 Illness duration and "state versus trait"

It has been demonstrated in patients with Alzheimer's disease that inconsistent results—increased, reduced and normal SP—can be organised into a logical pattern, in accordance with the time course of the disease; SP is initially increased, followed by reduced SP (Giffard et al., 2002). The variable results in schizophrenia might be similarly related to the duration of illness. In a longitudinal study, Gouzoulis-Mayfrank et al. (2003) found no correlation between the magnitude of SP and length of illness or number of previous psychotic episodes. Moritz and colleagues (2001b; 2001a; 2002) and Chenery et al. (2004) also found no correlation between direct or indirect SP and length of illness, although Maher et al. (1996) found a negative correlation between direct SP and the length of illness in a cross-sectional study. Unlike the pattern of SP results found in Alzheimer's disease, SP in schizophrenia does not seem to deteriorate over the course of the illness.

Gouzoulis-Mayfrank et al.'s (2003) study sheds light on additional reasons for the heterogeneous results across studies. They found the increased direct SP to be state-dependent; it was present in patients with thought disorder only during the acute psychotic state. However, normal SP was found in the same group of patients after their thought disorder and other positive symptoms had resolved. The authors conclude that SP in patients with thought disorder is "state-

dependent and might be viewed as an episode marker of psychosis with thought disorder" (Gouzoulis-Mayfrank et al., 2003).

1.2.10 Alternative approaches

One of the main limitations in research in schizophrenia is that it has not been possible to clearly distinguish between the direct effects of underlying pathology and the deficits that indirectly result from the long-term experience of schizophrenia symptoms, and the inevitable related changes (e.g. hospitalisation, prolonged use of antipsychotic medication, and possible decline in intellectual functioning). The two main approaches to circumventing this difficulty are *(i)* employing pharmacological models of psychosis in healthy volunteers (these studies are reviewed in section 1.3), and *(ii)* comparing healthy individuals with low and high schizotypy trait scores.

Some studies focus on differences between low and high "schizotypes" i.e. healthy individuals with low and high schizotypy scores, the latter being considered more 'prone' to psychosis. Schizotypal personality traits can be defined as tendencies to behave and think in ways that are qualitatively similar to features seen in schizophrenia (Steel et al., 2007). Schizotypy is usually measured using the Oxford-Liverpool Inventory of Feelings and Experiences questionnaire (O-LIFE; Mason et al., 1995). Morgan et al. (2006a) based their selection criteria for low and high schizotypy groups on pilot work, with participants from bottom and top 10th percentile of O-LIFE scores being allocated to each group, respectively. At a short SOA, the high schizotypy group showed reduced SP compared with low schizotypes; the pattern was reversed at a long SOA. No deficits specific to low frequency words were identified in relation to schizophrenia-like traits. Differences in SP were not coupled with differences in explicit semantic memory assessments (Morgan et al., 2009b).

Instead of comparing groups of high and low schizotypes, Johnston et al. (2008) conducted a purely correlational study between O-LIFE subscale scores and direct

and indirect SP tasks, with short and long SOAs. They found that increased indirect SP at a short SOA was associated with increased O-LIFE Cognitive Disorganisation (index of thought disorder) scores. However, as an exact p value for this correlation was not reported, it is not clear whether this correlation would survive correction for multiple comparisons. Considering the high number of correlations conducted—4 SP effects and 4 O-LIFE subscale scores—it is surprising that no other correlations were found. In summary, research based on schizotypy traits has not yet provided clarification on SP findings in schizophrenia.

1.2.11 Electrophysiological correlates of semantic priming

LD tasks have been employed to investigate the electrophysiological correlates of language function in schizophrenia (Table 1.2), using electroencephalography (EEG). Most of the research in this area has focused on event-related potentials (ERPs) and their components: the positive peak P200, the negative peak N400 and the late positive component (LPC).

P200 is a positive component of the ERP, usually peaking between 140 and 320 ms after the target (Hokama et al., 2003; Koyama et al., 1991; Koyama et al., 1994). The N400 peak, also referred to as N350 in Hokama et al. (2003), and N370 in Koyama et al. (1991; 1994), is a negative component of the ERP that peaks around 400 ms after the target presentation (Condray et al., 1999; Condray et al., 2003; Kostova et al., 2003a; Kostova et al., 2003b; Kostova et al., 2005). The N400 amplitude is thought to be inversely proportional to the degree of the predictability of a word, based on previous context (Niznikiewicz et al., 1997). In the LD paradigm, N400 is usually of lower amplitude when the prime is related to the target, compared with when it is unrelated or when the target is not a real word. This difference in N400 amplitude is denoted as the N400 effect and is thought to reflect processes involved in contextual integration (Kutas & Federmeier, 2000). Most studies are based on scalp EEG recordings that have a poor spatial resolution and therefore cannot tell us precisely where the N400 effect is occurring.

Table 1.2 Summary of electrophysiological studies of semantic priming in schizophrenia

Study	Participants	SOA/RP	P200		N350/N370/N400			P300/LPC		
			Amplitude	Latency	Amplitude	N400 effect	Latency	Amplitude	SP effect	Latency
Koyama et al. (1991): P200/ N370/ N400 effect/ LPC	8SZ(M) 23HC	1000/33	LT: M > HC	M > HC	M = HC	M = HC Fz: M < HC Cz: M < HC†	M > HC	R: Fz: M > HC		M = HC
Koyama et al. (1994): P200/ N370/ LPC/ CNV	20SZ(M, UM) 23HC	1500/33	SZ = HC	Fz: SZ > HC	SZ = HC	Fz: SZ < HC	Cz: SZ > HC	SZ = HC Fz: SZ < HC		Pz: SZ > HC
	11SZ(M, UM) 11HC			SZ = HC			SZ = HC	Cz, Pz: SZ > HC		SZ = HC
Condray et al. (1999; 2003): N400/ P300	37SZ(M, UM) 34HC	350/31&63 950/31&63			SZ = HC	Oz, Cz: SZ < HC Fz: M = HC UM < HC	M > HC	SZ < HC	SZ < HC	SZ = HC
Hokama et al. (2003): P200/ N350/ N400 effect/ LPC	18SZ(UM) 18HC	1500/33	UM = HC O1: UM < HC	UM = HC	Ps: UM > HC	UM < HC	UM > HC	UM < HC		UM > HC
Kostova et al. (2003a): N400/ LPC	38SZ(TD, M) 24HC	450/16.7&33			R: TD(M) > HC	TD(M) < HC		U: TD(M) < HC	TD(M) < HC	
Kostova et al. (2003b): N400	12SZ(M) 12HC	450/16.7			M > HC	M < HC				

Kostova et al. (2005): N400	50SZ(M) 40HC	450/16.7			M > HC	M < HC TD↑ N400 effect↓				
Kiang et al. (2008): N400	16SZ(M) 16HC	300&750/67*			R: SZ > HC U: SZ = HC	SZ < HC	SZ = HC			

All studies employed lexical decision tasks.
Participants: SZ – schizophrenia patients; **M** – medicated SZ; **UM** – unmedicated SZ; **TD** – SZ with thought disorder; **HC** – healthy controls.
Electrode sites: RT, LT – right and left temporal sites; **Ps** – posterior sites.
Task conditions: R – related word pairs, **U** – unrelated word pairs.
SOA – stimulus onset asynchrony (in ms); **RP** – relatedness proportion (in %).
* Half of the related pairs were directly related and other half indirectly related.
† At a trend level.

However, intracranial recordings, from electrodes implanted into the brains of epilepsy patients, have shown that the main generators of N400 to visually presented words are located in the ventral and anterior temporal lobe and in the inferior prefrontal cortex (Halgren et al., 1994). The LPC, also referred to as the P300 in Condray et al. (1999; 2003), follows N400. It seems to be related more to syntactic function and attentional processes related to language than to semantic processing (Osterhout et al., 1997).

Similar to the behavioural data, there are inconsistencies between electrophysiological studies on SP effect in schizophrenia. A finding that seems consistent over studies employing LD tasks is that the N400 effect is reduced in magnitude or absent in people with schizophrenia compared with healthy people (Condray et al., 1999; Condray et al., 2003; Hokama et al., 2003; Kiang et al., 2008; Kostova et al., 2003a; Kostova et al., 2003b; Kostova et al., 2005; Koyama et al., 1991; Koyama et al., 1994). Some of the evidence points to increased N400 amplitude in the related condition, as opposed to a reduced N400 in the unrelated condition (Kiang et al., 2008; Kostova et al., 2003a; Kostova et al., 2003b; Kostova et al., 2005). Other studies have not found increased N400 amplitude in schizophrenia (Condray et al., 1999; Condray et al., 2003; Koyama et al., 1991; Koyama et al., 1994).

Most studies that investigated N400 latency show that it is prolonged in schizophrenia; this is usually coupled with patients' slower RTs, and reflects slowed information processing (Condray et al., 1999; Condray et al., 2003; Hokama et al., 2003; Koyama et al., 1991; Koyama et al., 1994). Longer latencies in schizophrenia have also been found for P200 (Koyama et al., 1991; Koyama et al., 1994) and LPC (Hokama et al., 2003; Koyama et al., 1994). However, when Koyama et al. (1994) matched subgroups of schizophrenia patients and healthy controls for similar RTs, the differences in P200, N400 and LPC latencies between the two groups were not significant. Some studies found no abnormalities in P200 (Hokama et al., 2003) or LPC latencies (Condray et al., 1999; Condray et al., 2003; Koyama et al., 1991) in patients although the

patients' RTs were significantly longer. Furthermore, Kiang et al. (2008) found no differences in N400 latency; RTs were not reported in this study.

Therefore, the most consistent finding of the ERP studies is the reduced N400 effect in schizophrenia. The reduced N400 effect is usually interpreted as a deficit in utilisation of context in people with schizophrenia, resulting in undifferentiated processing of related and unrelated words (e.g. Hokama et al., 2003). If the reduced N400 effect in schizophrenia is an indicator of reduced capability to utilise context, it should be coupled with reduced behavioural SP effect. Kostova et al.'s (2003b) study has indeed found reduced behavioural SP in their schizophrenia patients group, paralleling the reduced N400 effect in the same group. However, as discussed above, reduced SP in schizophrenia is not the most common finding.

As with behavioural results, it is possible that the heterogeneity of schizophrenia symptoms underlies the disparity in ERP findings. For instance, the ERP components seem to be related to the degree of thought disorder; the N400 amplitude in the related condition increases with thought disorder—thus reducing the N400 effect—while the LPC amplitude in the unrelated condition and the LPC effect decrease with thought disorder, both regardless of the relatedness proportion (Kostova et al., 2003a; Kostova et al., 2005).

In comparison, the effect of medication on ERP components is not clear (Table 1.2). Most of the studies included either only medicated patients or a mixture of medicated and unmedicated patients. However, all patients were unmedicated in Hokama et al.'s (2003) study, which indicates that the reduced N400 effect and prolonged latencies that are found in other studies with medicated patients are not due to medication effects. The reduced N400 effect in unmedicated patients was also found by Condray et al. (2003). This review included only LD SP studies. Other language tasks have been employed to investigate electrophysiological correlates of semantic processing in schizophrenia; these have also produced a mixture of results, but confirmed the abnormal N400 effect (for a review see Kumar & Debruille, 2004).

1.2.12 Discussion

As discussed in this review, SP findings in schizophrenia are highly variable. The reasons for discrepancies have been debated for almost twenty years, without a consensus being reached to date. This review has established that there are two main variables, which robustly underpin differing SP results in schizophrenia. First, the relatedness proportion effect, where low proportions of related prime-target pairs result in reduced or normal SP, whilst higher proportions lead to increased SP in people with schizophrenia compared with healthy people. Second, using indirectly related prime-target pairs—especially at short SOAs—results in enhanced SP in schizophrenia. These results are often interpreted within the framework of the spreading of activation model to mean that there is faster automatic spreading of activation, which, in turn, might be one of the causes of language deficits found in schizophrenia.

In the framework of distributed network models, these results indicate that the patterns of concept representations overlap more between different concepts in people with schizophrenia compared with healthy people. Consequently, patterns of activation of different concepts resemble each other more, and since the processing of a target begins from the pattern created by the processing of its prime, this results in enhanced SP in schizophrenia. Finally, there is some indication that prominent thought disorder in schizophrenia might be related to increased SP.

Future SP studies should address the confounds of research in schizophrenia summarised in this review. The participant selection criteria should be carefully specified to avoid a highly heterogeneous sample, unless correlational analyses with symptoms are planned. However, in practice it is very difficult to circumvent all of the confounds in schizophrenia SP research, especially the psychometric artefacts. Finally, task parameters, especially the SOA and the relatedness proportion should be carefully considered, to distinguish as clearly as possible between automatic and strategic processes.

1.3 Literature review II: pharmacological manipulations of semantic priming

SP studies employing pharmacological manipulations have primarily targeted dopaminergic neurotransmitter system. Kischka et al. (1996) investigated dopaminergic modulation of direct and indirect SP using L-Dopa (the amino acid L-3,4-dihydroxyphenylalanine), a dopamine precursor. L-Dopa significantly reduced indirect SP at a long SOA, while no indirect SP was obtained in the placebo and L-Dopa groups at a short SOA. Although the decrease in direct SP was not statistically significant in the L-Dopa group, numerically it showed a similar pattern to indirect SP.

Copland et al. (2003a) used a SP task with targets related either to a dominant or a subordinate meaning of a homonym prime in related pairs (see section 1.2.4). At a long SOA, L-Dopa diminished SP for both the dominant and the subordinate targets, while at short SOA only SP for dominant targets remained significant. The authors of both studies interpreted their findings in support of the view that dopamine increases signal-to-noise ratio. The dopaminergic system is thought to have a modulatory role whereby it amplifies stronger signals, and dampens weaker signals (Cohen & Servanschreiber, 1992). This leads to more 'focused' processing, therefore reducing the hypothetical automatic spreading of activation in the semantic network (see section 1.1). However, as the L-Dopa effects were most pronounced at long SOAs in both studies, it is more likely that the modulation of SP reflected changes in strategic processing rather than on automatic levels. Furthermore, Angwin et al. (2004) also found that L-Dopa modulated SP only at a long SOA, while no modulation was found at shorter SOAs. There was no differential modulation of direct and indirect SP.

L-Dopa is a non-selective dopamine receptor agonist; consequently it is not clear whether SP modulation was due to its effect on D_1 or on D_2 receptors. Roesch-Ely et al. (2006) attempted to distinguish between D_1 and D_2 receptor agonist effects. In the absence of a selective D_1 receptor agonist availability, they used a subtraction design with bromocriptine (D_2 receptor agonist) and pergolide

(D_1/D_2 receptor agonist). Any effect achieved by pergolide and not bromocriptine would presumably be due to D_1 receptor occupancy. However, neither bromocriptine nor pergolide had an effect on direct and indirect SP when SP was calculated in relation to unrelated prime-target pairs. Based on their previous work (Weisbrod et al., 1998), however, the authors suggest that RTs to unrelated pairs are not an appropriate baseline due to the lateralisation effect on these. Instead, they proposed using pairs in which primes and targets are identical. Using this baseline, they found a trend toward decreased indirect SP in the right visual field in the pergolide group, which was not present in the bromocriptine group. Considering the non-standard baseline, these results require replication using a different task. Furthermore, as with their previous study (Weisbrod et al., 1998), primes were centrally presented and therefore processed by both hemispheres (see section 1.2.5).

More recently, Copland et al. (2009) investigated modulation of haemodynamic responses during a SP task by L-Dopa using fMRI. Similar to their behavioural study (Copland et al., 2003a), L-Dopa had no effect on SP for dominant targets, while it diminished SP for subordinate targets at a short SOA. The placebo group showed SP for both targets. The lack of subordinate SP in the L-Dopa group was paralleled by a decrease in haemodynamic response to subordinate targets in bilateral anterior cingulate and the left middle frontal gyrus. Middle frontal gyri are thought to be implicated in automatic SP (Kotz et al., 2002; Rissman et al., 2003); anterior cingulate however is thought to be involved in strategic processing (Copland et al., 2007; Mummery et al., 1999; Rossell et al., 2001). Future studies should distinguish between the dopaminergic modulation of haemodynamic responses involved in automatic and strategic processing; Copland et al.'s (2009) task did not include a long SOA or a relatedness proportion manipulation.

In contrast to studies on dopaminergic-related modulation of SP, only one study has investigated glutamatergic-related changes. Morgan et al. (2006b) examined the effects of ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, acutely in healthy volunteers and following chronic self-administration in

recreational ketamine users. Their task manipulated *(i)* SOA to theoretically distinguish between automatic versus strategic processing and *(ii)* word frequency. Word frequency manipulation has been used in SP research (Rossell & David, 2006) to differentiate impairments in access to the semantic store and degradation of the semantic store. It has been shown that patients with semantic dementia 'lose' low frequency words first when their semantic store starts to degrade, which is later followed by the loss of high frequency words (Lambon Ralph et al., 1998; Warrington & Cipolotti, 1996). In theory, there are no differential impairments for low and high frequency words when access is disrupted.

Therefore, reduced SP for both low and high frequency words indicates access impairments, while reduced SP for low but not for high frequency words indicates semantic store degradation. Morgan et al. (2006b) found that acute administration of ketamine produced a dose-dependent impairment of SP at a long SOA, whereby the RTs for related word pairs were longer than for the unrelated word pairs—the effect they referred to as 'inverse' SP. There was no frequency effect, indicating that SP changes were due to impaired access to the semantic store. Changes induced by chronic ketamine were similar, however, the effect was confined to low frequency words, indicating a possible degradation of the semantic store.

Last, Spitzer and colleagues conducted two studies (Gouzoulis-Mayfrank et al., 1998; Spitzer et al., 1996) that investigated serotonergic-related modulation of SP at short SOAs. They employed psilocybin, a hallucinogenic drug, which gets metabolised to psilocin immediately after ingestion; psilocin is a partial 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptor agonist and thus mimics the effects of serotonin (Roth et al., 1998; Vollenweider et al., 1998). Spitzer et al. (1996) found an increase in indirect SP when participants were on psilocybin compared to pre-drug testing. Gouzoulis-Mayfrank et al. (1998) also found a trend for increased indirect SP after psilocybin. However, there was no SP obtained overall. Interpretation of the data from these studies is limited for the following reasons: *(i)* small groups: 8 and 7 participants in Spitzer et al.'s and Gouzoulis-

Mayfrank et al.' studies, respectively; *(ii)* unclear procedure and statistical analyses, and most importantly *(iii)* comparisons between placebo and psilocybin did not reach statistical significances.

To conclude, the majority of pharmacological SP studies focused on dopaminergic modulation while only one study investigated the effects of glutamatergic modulation on SP. The next two chapters in this thesis therefore explore the effects of NMDA receptor antagonist administration—acutely to healthy volunteers (chapter 2), and repeatedly as seen in recreational ketamine users (chapter 3).

Chapter 2: Effects of acute ketamine on semantic priming

Almost every known neurotransmitter and neuromodulator, from glutamate and GABA through to dopamine and serotonin has at one time or another been proposed as 'the cause' of schizophrenia, only to disappear again as some new fashion sweeps the trade.

Steven Rose (2005, pp. 237)

2.1 Introduction

Our knowledge, ideas and meanings of words are thought to be stored in the semantic memory system (Schacter et al., 2000). Semantic memory disturbances have long been thought to underlie some of the schizophrenia symptoms (Gouzoulis-Mayfrank et al., 2003; Rossell et al., 1999; Sumiyoshi et al., 2005) and the semantic priming (SP) paradigm has often been employed to investigate this premise. As reviewed in chapter 1, there has been a considerable number of SP studies conducted with schizophrenia patients (for additional reviews see Minzenberg et al., 2002; Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007). It has been difficult not only to clarify which symptoms are related to changes in semantic memory function, but also to distinguish direct effects of underlying psychopathology in schizophrenia from the secondary changes that result indirectly from the illness.

Instead of directly testing schizophrenia patients, an alternative approach is to employ pharmacological models that reproduce some of the acute psychotic symptoms in healthy individuals. The first advantage of this method is that there is no interference from secondary changes in schizophrenia, thus controlling for the indirect effects. Second, between-subject variability is eliminated because it is possible to test the same individual before, during and after the administration of a drug. Third, pharmacological manipulations advance our understanding of biological substrates of acute psychosis. Last, they allow a symptoms-orientated approach.

There are several pharmacological models of acute psychosis known to produce schizophrenia-like symptoms. While each of these models mimics some of the symptoms, none reproduce the full spectrum of symptoms found in schizophrenia and thus, all are far from ideal (for a review see Potvin et al., 2005). For example, amphetamine-induced psychosis mimics well the positive symptoms, but not the negative symptoms of schizophrenia. Hence, depending on which symptoms a study attempts to investigate, a particular pharmacological model should be employed. The current study is primarily concerned with semantic memory function, so the acute ketamine administration model was chosen as it induces thought disorder and frontal cognitive deficits. Effects of chronic administration of ketamine in recreational users are investigated in chapter 3.

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist which, when administered, interferes with normal glutamate and aspartate function (Anis et al., 1983). NMDA receptors are most densely located in the prefrontal cortex and the hippocampus, areas critically involved in higher executive functions and memory (Monaghan et al., 1989). Acutely, NMDA receptor antagonists induce reliable dose-related positive and negative schizophrenia-like symptoms in healthy volunteers, including cognitive symptoms (for a review see Newcomer & Krystal, 2001).

The induced symptoms include delusions (Krystal et al., 1994; Krystal et al., 1998; Krystal et al., 2005), hallucinations (Krystal et al., 1994; Vollenweider et al., 1997), thought disorder (Adler et al., 1998; Adler et al., 1999; Krystal et al., 1994; Krystal et al., 1998; Malhotra et al., 1996; Vollenweider et al., 1997) and emotional withdrawal (Krystal et al., 1994; Krystal et al., 1998; Malhotra et al., 1996; Vollenweider et al., 1997). The nature of these ketamine-induced changes, as well as of other NMDA receptor antagonists, has added support to the NMDA receptor hypofunction model of schizophrenia (Carlsson & Carlsson, 1990; Farber, 2003; Javitt & Zukin, 1991; Kornhuber et al., 1989; Olney et al., 1999; Tamminga et al., 2003). Furthermore, when administered to stabilised patients

with schizophrenia, NMDA receptor antagonists exacerbate their symptoms, regardless of whether they are on neuroleptics or not (Allen & Young, 1978; Lahti et al., 1995a; Lahti et al., 1995b; Malhotra et al., 1997). The symptoms induced by ketamine in schizophrenia patients closely resemble the symptoms experienced during their individual acute episodes (Lahti et al., 1995a; Malhotra et al., 1997).

SP studies that employed pharmacological manipulations are reviewed in detail in section 1.3. Briefly, the only study (Morgan et al., 2006b) that has investigated the effects of acute ketamine administration on SP has found that it impairs SP at a long stimulus onset asynchrony (SOA). Acute ketamine reversed the typical SP effect: response times (RTs) for related word pairs were longer than for the unrelated word pairs ('inverse' SP). One of the potential explanations of their findings could be the modulation of the effects of related primes on the processing of the target (facilitation) or the effect of unrelated primes on the target (inhibition). Facilitation refers to faster RTs for related word pairs relative to a baseline while inhibition refers to slower RTs for unrelated pairs than for baseline. To look at facilitation and inhibition, therefore, one needs a 'neutral' condition that serves as a baseline in which targets are preceded with a 'neutral' prime, which elicits minimal, if any facilitation and/or inhibition of the target (e.g. prime word *blank* followed by a target word; de Groot et al., 1982). Facilitation is thought to reflect both automatic and strategic processes, while inhibition relies more upon strategic processing (c.f. Minzenberg et al., 2002).

The first aim of the present study was to determine whether ketamine modulates facilitation or inhibition within a SP task. The second aim was to clarify whether any modulation was taking place at automatic and/or strategic levels. To maximally distinguish between automatic and strategic processing, two distinct conditions were created. In line with previous research (Lecardeur et al., 2007), these conditions manipulated both the SOA and the relatedness proportion. A long SOA and high relatedness proportion are thought to promote the strategic process of expectancy (section 1.1); the individual internally generates predictions about which words will appear after a given prime, that is, they

generate a set of words related to the prime word. When a related target word appears, it is recognised more easily, while the reverse is true for unrelated targets (e.g. Becker, 1980). Additionally, when there is a large number of related word pairs (i.e. the relatedness proportion is high), the relationship between the prime and the target words is actively utilised to bias lexical decision-making, in a process known as semantic matching (e.g. Neely & Keefe, 1989). The presence of a semantic relationship between the prime and the target words produces a 'real word' bias for the target, i.e. if the words are related, the target must be a real word. Conversely, there is a 'non-word' bias for unrelated pairs. The 'strategic' condition, therefore, used a long SOA and high relatedness proportion. Accordingly, the 'automatic' condition had a short SOA and low relatedness proportion.

The first task investigated direct SP in which the primes and targets are strongly (directly) related, for example, the prime word *lion* is directly related to the target word *tiger*. To date, no study using the ketamine model has investigated its effects on indirect SP. In indirect SP, words are related to each other via a mediator word that is not presented. For example, the prime word *lion* and target word *stripes* are related to each other via a mediator word *tiger*. Indirect SP has produced some of the most robust and substantial differences in SP in schizophrenia, especially at short SOAs (for reviews see chapter 1; Rossell & Stefanovic, 2007).

The present study also investigated the effect of acute ketamine on indirect SP. Some studies have failed to find indirect SP (e.g. Balota & Lorch, 1986; de Groot, 1983) using a standard lexical decision (LD) task. The indirect SP task chosen was based on a previous study that successfully obtained indirect SP (Chwilla et al., 2000). A pattern that emerged from previous studies on indirect SP indicated that it is more reliably obtained when the indirectly related pairs are in separate blocks from directly related pairs. This may be because participants treat indirectly related pairs as unrelated when the directly related pairs are present, which in turn leads to a 'non-word' bias (McNamara & Altarriba, 1988).

Increased direct SP due to increased facilitation and inhibition were expected in the strategic condition relative to the automatic condition (e.g. Lecardeur et al., 2007) in the placebo group. In contrast, based on Morgan et al. (2006b), I predicted that acute ketamine would selectively reduce direct SP in the condition tapping strategic processes. Following from this, I expected that there would be a lack of inhibition of unrelated word pairs in the strategic condition in the ketamine groups. In addition, ketamine was expected to abolish the difference in facilitation of related pairs between automatic and strategic conditions. Based on schizophrenia studies (section 1.2), I speculated that the indirect SP task might be more sensitive to acute ketamine effects at automatic levels of processing than the direct SP task.

2.2 Methods and materials

The current study was approved by the UCL/UCLH Ethics Committee and was carried out in accordance with the Declaration of Helsinki. All participants gave written, witnessed, and informed consent.

2.2.1 Participants and design

An independent group design with double-blind procedures was used in which male and female participants were randomly assigned to one of the three groups: placebo, low-dose (target plasma level: 75 ng/ml) and high-dose (target plasma level: 150 ng/ml) ketamine. Groups were balanced for gender (50% female). Volunteers aged 18-35 years were recruited through an advertisement and were paid for participation. Participants were native English speakers with no history of *(i)* serious medical conditions, *(ii)* personal or family mental health diagnosis, or *(iii)* substance misuse.

All participants attended a screening session prior to the experimental day. In total, 82 volunteers responded to the advertisement, 58 meeting the inclusion criteria participated, 10 dropped out (1 after cannulation due to faintness and 9 on the high dose due to adverse effects, which included 3 due to nausea, 5 who were unable to concentrate or did not wish to continue, and 1 due to high blood pressure). Forty-eight participants completed the testing session.

2.2.2 Drug administration

Two 20-gauge intravenous cannulae—one for the infusion and the other for blood samples—were inserted into participant's forearms before pre-infusion/baseline testing; 1 litre of Hartmann's solution (Baxter Healthcare Ltd, Norfolk, UK) was administered over 2 hours. Ketamine administration was via a Graseby 3400 intravenous infusion pump (Smiths Medical International, Watford, UK), externally controlled by the Stan-pump computer software program (available free of charge from Dr S. Shafer MD on http://anesthesia.stanford.edu/pkpd/, accessed November 27, 2006). The program uses a bolus-elimination-transfer infusion scheme based on the Clements pharmacokinetic model (Clements et al., 1982). A steady state of predicted plasma ketamine concentration according to the model was achieved over a period of 12 minutes. Ketamine levels were maintained by a continuous administration during the testing.

Initially the low and high doses of ketamine administered were 100 ng/ml and 200 ng/ml. However, due to dropouts (5 out of 7 participants on 200 ng/ml), these were reduced to 75 ng/ml and 150 ng/ml. One participant given 100 ng/ml and 2 given 200 ng/ml were included in the low-dose and high-dose groups in the final analysis; all others received 75 ng/ml or 150 ng/ml. Peripheral venous blood samples were taken at 6 and 45 minutes after achieving the steady state to determine ketamine and norketamine concentrations in the blood (all blood samples were from the 75 ng/ml and 150 ng/ml groups). Plasma was obtained immediately by centrifugation and stored at -80C. Ketamine and norketamine levels were measured using gas chromatography (C3P Analysis Lab, Plymouth, UK).

2.2.3 Procedure

All participants attended a screening session and a testing session, which were conducted on separate days. The National Adult Reading Test (NART; Nelson, 1982), a 24-item expanded Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986), Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and Beck Anxiety

Inventory (BAI; Beck & Steer, 1990) were administered during the screening session. The Oxford-Liverpool Inventory of Feelings and Experiences questionnaire (O-LIFE; Mason et al., 1995) was also included as a measure of trait schizotypy. Self-reports of abstinence from recent drug use were verified using a urine test. Participants were required to *(i)* abstain from use of alcohol for 24 hours prior to the testing session, *(ii)* to fast for morning testing from midnight, and for afternoon testing for > 6 hours beforehand, and *(iii)* to refrain from drinking for > 2 hours before the testing session.

On the testing day, after cannulation, baseline blood pressure and heart rate measures were recorded; the participant then underwent pre-infusion/baseline assessments. This was followed by the start of the infusion. When the target plasma concentration was theoretically achieved, testing began during the continuous infusion. The indirect SP and fluency tasks, as well as the subjective effects questionnaires, were completed both pre- and during the infusion. The direct SP and generation of opposites tasks were completed only once, during the infusion. The indirect SP task and the automatic direct SP condition were designed to minimise strategic processing and were thus administered before the strategic direct SP condition, to avoid interference. Other tasks (e.g. hinting task and superstitious conditioning task) were also administered but are not included here. After testing, participants were provided with light refreshments and discharged, depending on their 'street readiness'.

2.2.4 Assessments

All cognitive tasks (direct and indirect SP tasks, verbal and category fluency tasks, and the generation of opposites task) had two matched versions and the order of their administration was counterbalanced across groups. For each SP task, word lists in two versions were matched for word length, Kucera-Francis word frequency (Kucera & Francis, 1967), concreteness and imageability, and included nouns and verbs.

The relatedness between two words was determined using the Edinburgh Associative Thesaurus (EAT; Kiss et al., 1973). In both SP tasks, non-words were

taken from the ARC non-word database and were pronounceable, legally spelled sets of letter strings, matched for mean number of letters to real word targets (Rastle et al., 2002). The SP tasks were programmed using Presentation® software (http://www.neurobs.com).

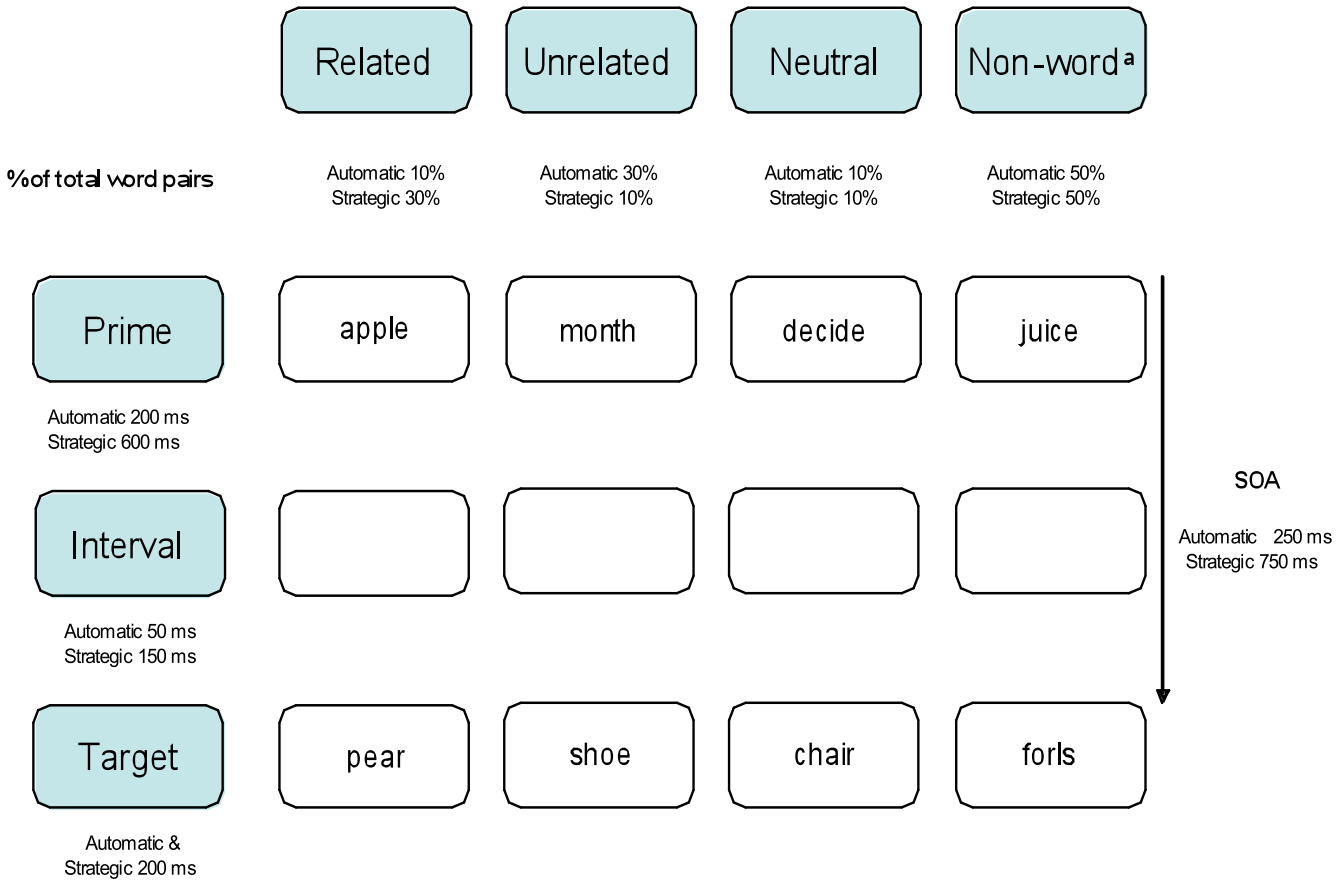
2.2.4 (i) Direct semantic priming task

The SOAs in the automatic and strategic conditions were 250 ms and 750 ms, respectively (for details see Figure 2.1). In line with Lecardeur et al. (2007), the relatedness proportions were 10% and 30% in the automatic and strategic conditions, respectively. In contrast to Lecardeur et al., 10% of pairs that included a non-word target had a neutral prime. The automatic condition consisted of 240 pairs: 24 related words, 72 unrelated words, 24 neutral prime - real word targets, and 120 with non-word targets (out of which 12 pairs had a neutral prime).

In the strategic condition there were 200 pairs: 60 related words, 20 unrelated words, 20 neutral prime - real word targets, and 100 non-word targets (out of which 10 had a neutral prime). The words in the related pairs were semantically and/or associatively related (appendix A). Only word pairs with association values > 10 in the EAT were included as directly related pairs.

The neutral prime was the verb *decide*. Participants were instructed to read the first word (prime) and to decide whether the second word (target) was a real word or not as quickly and as accurately as possible (LD task). They were also told that some pairs would include the word *decide* in order to remind them of what they should be doing, that is, decide whether the next set of letter strings is a real word or not. They indicated their response by pressing the corresponding key: 'yes' - it is a real word, 'no' - it is not a real word).

Figure 2.1 Direct semantic priming task employed in the ketamine studies



All stimuli were centrally presented. Primes were preceded by a fixation cross for 250 ms and a blank screen for 200 ms. The response window was set to 2000 ms, after which next trial was initiated. [a] 5% of total word pairs had a neutral prime (decide) followed by a non-word target; the remainder of non-word pairs had a real word prime. **SOA** – stimulus onset asynchrony.

2.2.4 (ii) Indirect semantic priming task

Indirect SP task parameters limited strategic processing to obtain indirect SP more reliably (Chwilla et al., 2000; Chwilla & Kolk, 2002). The prime and the target were presented simultaneously (SOA of 0 ms). A fixation cross appeared centrally for 400 ms, followed by the prime and the target above and beneath the fixation cross for another 400 ms. The response window was 2000 ms. In line with Chwilla et al. (2000), the relatedness proportion was low (16.7%): from 300 pairs, 50 were indirectly related word pairs, 100 unrelated word pairs, and 150 contained a non-word.

For the non-word pairs, non-words were at the top of the screen half of the time, and at the bottom the other half. The indirectly related word pairs were related through an intermediary word to which both the prime and the target were directly related (appendix B). Indirectly related pairs had an association value of less than 10 in the EAT. Participants were instructed to decide whether both the prime and the target were real words or not (double LD), as quickly and as accurately as possible, and indicate their answer by pressing a corresponding key ('yes' or 'no').

2.2.4 (iii) Fluency tasks and the generation of opposites task

In the verbal fluency task, participants were asked to generate as many words beginning with a given letter (*M* or *B*, depending on the version) as they could in 90 seconds, and to avoid saying words with a same prefix in a row (e.g. disinterested, disenchanted, dissatisfied) as well as proper nouns (i.e. names of people and places). In the category fluency task, participants were asked to list as many exemplars of a given category (*fruits* or *vegetables*, depending on the version) as they could in 90 seconds.

In the generation of opposites task, two lists, each containing 48 pairs of words with opposite meanings (e.g. *right* - *left*) from Curran and Hildebrandt (1999) were used to create two versions of the task by adapting them to contain only one word from the pair and the first letter of its opposite. These were read out

loud to participants and they were asked to name the opposite of each word starting with the first letter that was read to them.

2.2.4 (iv) Subjective effects

BPRS: In line with Krystal et al. (1998), selected BPRS items were rated during the infusion. These served to assess symptoms resembling those in schizophrenia: Positive Symptoms (4 items: suspiciousness, hallucinations, unusual thought content and conceptual disorganisation), Negative Symptoms (3 items: blunted affect, emotional withdrawal and motor retardation), Activation (3 items: tension, excitement, mannerisms and posturing), and Anxious Depression (6 items: somatic concern, anxiety, depression, guilt, motor retardation and tension).

The Psychotomimetic States Inventory (PSI; Mason et al., 2008) was used to index state schizotypy. PSI consists of 48 items that group into 6 subscales: Delusory Thinking, Perceptual Distortions, Cognitive Disorganization, Anhedonia, Mania and Paranoia.

The Adapted Dissociative States Scale (ADSS), adapted from Bremner et al. (1998) was also administered. ADSS consists of 19 subjectively measured items that refer to state dissociative symptoms with 3 subscales: Amnesia, Depersonalisation and Derealisation.

Subjective Effects Scale (SES), a visual analogue scale containing 19 items (Curran & Morgan, 2000), was employed to measure subjective effects in 3 main categories: Bodily Symptoms (dizziness, nausea or sickness, bodily numbness, unsteadiness and lack of co-ordination), Cognitive Symptoms (impaired concentration, depression, impaired memory and mental confusion), and Perceptual Symptoms (altered time perception, feelings of altered reality, visual distortion, distortion of sound and 'out of body' experiences).

2.2.5 Statistical analyses

In all SP tasks, participants with error rates higher than 20% were excluded. Incorrect trials or trials with RTs exceeding 2.5 standard deviations from a participant's mean RT, or with RTs shorter than 200 ms, or longer than 1500 ms were also excluded (c.f. Morgan et al., 2006b). RT criteria led to the exclusion of 3.3% and 3.4% of total trials in the direct and indirect SP tasks, respectively. For SP tasks, there was no effect of version, so results were collapsed across versions. To verify that SP in both tasks, as well as facilitation and inhibition in the direct SP task had occurred, separate paired-samples t-tests were performed on participants' mean RTs comparing the relevant word pairs (for SP: related versus unrelated word pairs; for facilitation: related versus neutral pairs; for inhibition: unrelated versus neutral pairs).

If these paired-samples t-test showed significant differences, group differences and possible interactions were explored. Separate 3 x 2 repeated measures analyses of variance (RMANOVAs) were performed on *(i)* the degree of SP (calculated as $RT_{unrelated} - RT_{related}$) for direct and indirect SP tasks, *(ii)* facilitation ($RT_{neutral} - RT_{related}$) for direct SP, and *(iii)* inhibition ($RT_{unrelated} - RT_{neutral}$) for direct SP, with Group (placebo, low-dose, and high-dose ketamine) as a between-subject factor and Condition (automatic versus strategic) for direct, and Time (pre-infusion versus during the infusion) for indirect SP as within-subject factors. Accuracy (% of correct trials) was analysed in a 3 x 2 RMANOVA with Group as a between-subject factor and Condition in direct, and Time in indirect SP task as within-subject factors. Post-hoc Bonferroni-corrected tests were conducted to explore any significant interactions.

For fluency tasks, the total number of words generated (total score), and the number of errors (repetition, general, semantic, and the total) were counted. Numbers of total errors were at floor levels in both tasks, so these data were not analysed further. Separate 3 x 2 RMANOVAs were performed for each fluency task with Group as a between-subject factor, and Time as a within-subject factor for total scores. In the generation of opposites task, the total number of correct answers was compared between Groups in a one-way ANOVA.

Subjective effects were analysed with 3 x 2 RMANOVAs with Group as a between-subject factor and Time as a within-subject factor. Where significant interactions emerged, *a priori* planned contrasts were conducted on change scores (during the infusion – pre-infusion/baseline) to compare *(i)* the placebo group to both ketamine groups and *(ii)* the low-dose to high-dose ketamine group.

The differences (during the infusion – pre-infusion/baseline) in ADSS and PSI total scores, the PSI Perceptual Distortions subscale and the PSI Cognitive Disorganisation subscale scores were calculated for each participant and correlated with direct and indirect SP in the ketamine groups, along with ketamine plasma levels. To reduce Type-I error, the alpha-level for correlations was set to 0.01.

2.3 Results

2.3.1 Demographics

There were no significant group differences in age, NART score, BPRS, BDI-II, BAI or O-LIFE (total score or individual subscales; Table 2.1).

Table 2.1 Demographic and background variables (mean, SD) for placebo, low-dose and high-dose ketamine groups

	Placebo	Low-dose	High-dose
Age	24.71 (4.47)	23.10 (3.18)	25.65 (4.29)
NART score	113.38 (5.24)	112.19 (4.13)	115.06 (4.42)
BPRS	27.56 (2.39)	28.50 (3.01)	26.69 (1.92)
BDI-II	5.47 (3.60)	5.94 (4.31)	3.88 (5.39)
BAI	3.75 (5.09)	2.44 (2.68)	2.94 (3.15)
O-LIFE	10.25 (5.15)	7.38 (5.14)	9.00 (6.43)

NART – National Adult Reading Test; **BPRS** – Brief Psychiatric Rating Scale; **BDI-II** – Beck Depression Inventory-II; **BAI** – Beck Anxiety Inventory; **O-LIFE** – Oxford-Liverpool Inventory of Feelings and Experiences.

Mean ketamine plasma concentrations were 39.37 ± 23.89 ng/ml in the low-dose group and 115.08 ± 54.72 ng/ml in the high-dose group, 6 minutes after the

steady state was achieved. At 45 minutes they were 54.64 ± 17.57 ng/ml in the low-dose group and 143.42 ± 60.67 ng/ml in the high-dose group. Mean norketamine plasma concentrations were 4.2 ± 6.32 ng/ml in the low-dose group and 12.17 ± 9.85 ng/ml in the high-dose group at 6 minutes; 22.24 ± 8.99 ng/ml in the low-dose group and 50.5 ± 32.62 ng/ml in the high-dose group at 45 minutes.

2.3.2 Assessments

2.3.2 (i) Direct semantic priming task

One participant from the placebo group was excluded from the analysis due to high error rate. In addition, one participant in the high-dose group did not complete the strategic condition due to nausea and was therefore excluded from the analysis.

Semantic priming effect (Table 2.2): a paired-samples t-test showed significantly shorter RTs for related word pairs (mean: 626.93 ± 70.38 ms) than for unrelated word pairs (mean: 646.92 ± 63.18 ms; t_{45} = - 4.95; $p < 0.001$), thus confirming that SP had occurred. SP effects ($RT_{unrelated}$ - $RT_{related}$) were calculated, and these data subjected to 3 x 2 RMANOVA. There was a trend towards a Group x Condition interaction ($F_{2, 43}$ = 2.56; p = 0.089) along with a trend for a main effect of Condition ($F_{1, 43}$ = 3.22; p = 0.08), which reflected more SP in the strategic condition (mean: 25.38 ± 36.96 ms) than in the automatic condition (mean: 14.59 ± 32.78 ms). Post-hoc tests exploring the Group x Condition trend showed higher SP in the strategic condition than in the automatic condition in the placebo group (p = 0.008; Figure 2.2). However, there were no significant differences between the automatic and strategic conditions in either the low-dose or high-dose ketamine groups. ***Facilitation:*** a paired-samples t-test showed that RTs for related word pairs were shorter than RTs for neutral word pairs (mean: 647.45 ± 62.84 ms; t_{45} = -4.43; $p < 0.001$), showing that facilitation had occurred.

Table 2.2 Mean (SD) accuracy and response times in the direct semantic priming task across the placebo and ketamine groups during the infusion

		Placebo	Low-dose	High-dose
Accuracy (%)				
Automatic Condition		95.28 (2.55)	95.23 (2.88)	93.39 (4.74)
Strategic Condition		95.10 (2.51)	95.84 (1.85)	94.23 (4.05)
Response times (ms)				
Automatic Condition	*Related*	625.54 (72.71)	652.26 (83.37)	636.99 (76.49)
	Unrelated	633.47 (62.30)	675.56 (78.46)	648.95 (54.85)
	Neutral	638.07 (66.25)	672.00 (75.41)	634.53 (53.24)
Strategic Condition	*Related*	602.14 (75.93)	621.73 (70.40)	621.58 (66.48)
	Unrelated	639.96 (87.10)	641.35 (66.58)	640.67 (64.36)
	Neutral	638.25 (74.15)	654.25 (70.97)	645.49 (80.54)

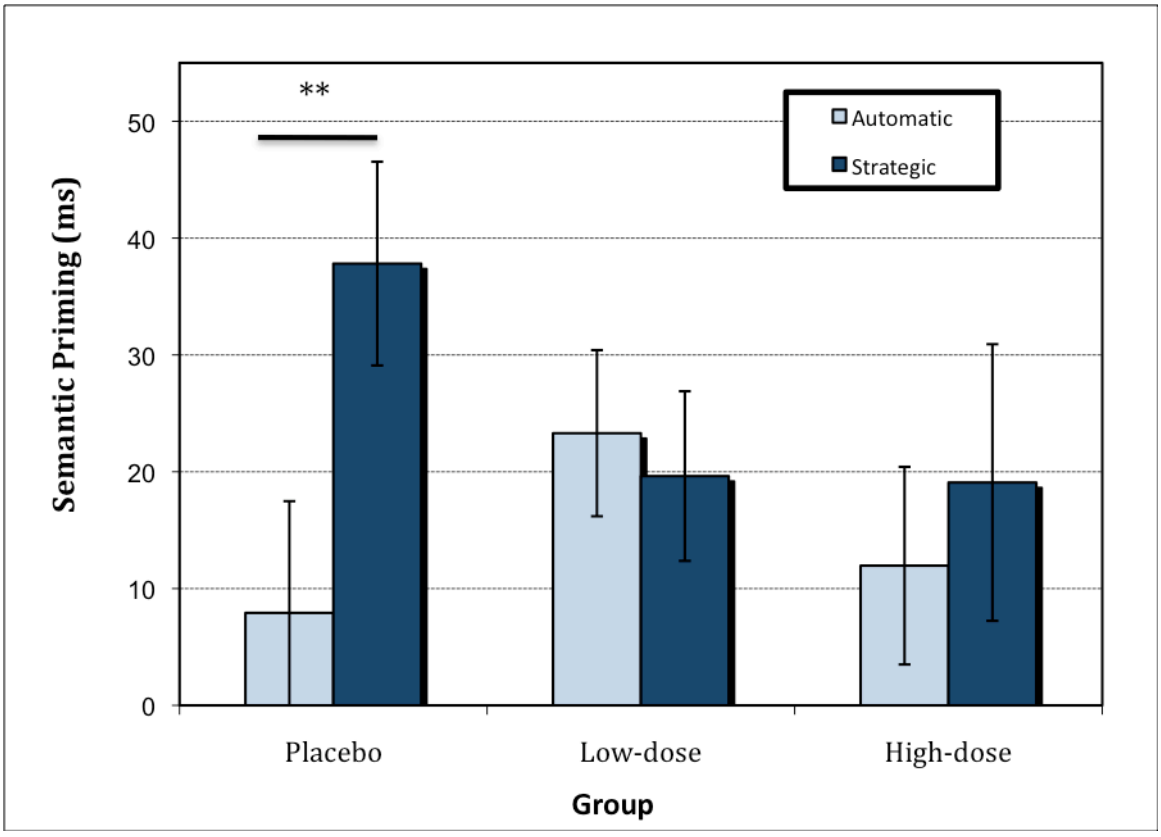


Figure 2.2 Direct semantic priming (RT unrelated - RT related) in the automatic and strategic conditions across the placebo and ketamine groups. Bars represent standard errors.

The 3 x 2 RMANOVA on facilitation showed a main effect of Condition ($F_{1, 43} = 6.6$; $p = 0.014$), whereby there was more facilitation in the strategic condition (mean: 30.89 ± 37.37 ms) than in the automatic condition (mean: 10.15 ± 45.27 ms). There were no group differences or interactions. ***Inhibition:*** there were no differences in RTs and, therefore, no evidence of inhibition. ***Accuracy*** (Table 2.2): there were no group differences or interactions.

2.3.2 (ii) Indirect semantic priming task

Three participants from the high-dose group and 1 from the placebo group were excluded due to high error rates. ***Semantic priming effect*** (Table 2.3): a paired-samples t-test showed significantly shorter RTs for indirectly related word pairs (mean: 802.46 ± 78.62 ms) than for unrelated word pairs (mean: 825.06 ± 81.53 ms; $t_{43} = -7.43$; $p < 0.001$), confirming that indirect SP had occurred. The 3 x 2 RMANOVA showed no Group effect or interactions. ***Accuracy*** (Table 2.3): the 3 x 2 RMANOVA on accuracy showed a trend towards a Group x Time interaction ($F_{2, 41} = 3.0$; $p = 0.061$). Post-hoc tests showed only a trend towards lower accuracy during the infusion compared to pre-infusion/baseline in the high-dose group ($p = 0.083$).

Table 2.3 Indirect semantic priming task: mean (SD) accuracy and response times across the placebo and ketamine groups pre- and during the infusion

		Placebo	Low-dose	High-dose
Accuracy (%)				
Pre-infusion		92.04 (3.96)	92.81 (4.48)	92.80 (5.28)
During the infusion		93.40 (3.25)	93.48 (4.15)	91.13 (6.10)
Response times (ms)				
Pre-infusion	*Related*	782.27 (82.37)	805.55 (103.83)	791.68 (92.39)
	Unrelated	802.83 (103.94)	832.21 (105.73)	808.72 (82.82)
During the infusion	*Related*	794.18 (88.21)	821.54 (85.68)	818.83 (74.07)
	Unrelated	820.42 (85.63)	848.02 (90.12)	835.32 (79.04)

2.3.2 (iii) Fluency tasks and the generation of opposites

Fluency tasks (Table 2.4): 3 x 2 RMANOVAs on total scores showed no significant main effects or interactions in either of the fluency tasks.

***Generation of opposites task*:** One participant from the high-dose group did not complete the task due to nausea. Data from the participants who have completed the task showed no significant group differences for total scores between the placebo group (mean: 44.19 ± 4.15), low-dose (mean: 44.25 ± 2.05) and high-dose ketamine groups (mean: 44.87 ± 2.03).

Table 2.4 Fluency tasks: mean (SD) total scores and errors across the placebo and ketamine groups pre- and during the infusion

		Placebo	Low-dose	High-dose
Verbal fluency				
Total errors	*Pre-infusion*	0.81 (0.91)	0.19 (0.40)	0.44 (0.89)
	During the infusion	0.50 (0.82)	0.25 (0.45)	1.00 (0.97)
Total score	*Pre-infusion*	19.06 (7.26)	20.31 (5.21)	20.06 (5.50)
	During the infusion	20.06 (6.94)	21.50 (5.73)	18.81 (4.86)
Category fluency				
Total errors	*Pre-infusion*	1.56 (2.83)	1.69 (4.43)	1.25 (2.21)
	During the infusion	1.88 (2.19)	2.19 (5.42)	1.75 (2.82)
Total score	*Pre-infusion*	19.38 (3.28)	17.50 (4.68)	19.00 (5.44)
	During the infusion	19.88 (4.35)	16.88 (5.44)	17.69 (6.04)

2.3.2 (iv) Subjective effects

Significant Group x Time interactions and contrasts on change scores (during the infusion – pre-infusion/baseline) are shown in Table 2.5. To summarise, the contrasts were highly significant, indicating clear dose-response effects of ketamine on the BPRS Positive Symptoms and Negative Symptoms, ADSS total score, and SES measures. In addition, there was a significantly higher increase in PSI total scores and PSI Perceptual Distortions (see Figure 2.3) and Cognitive Disorganisation subscales during the infusion in the ketamine groups compared with the placebo group.

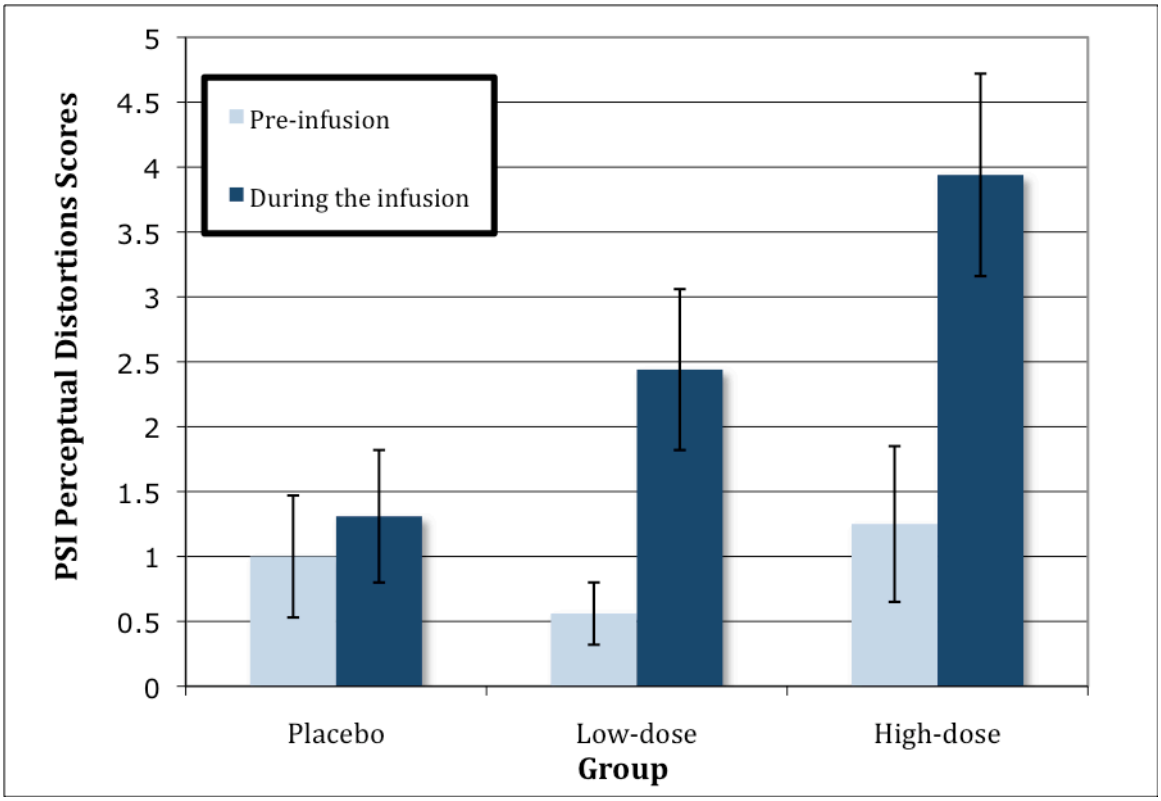


Figure 2.3 PSI Perceptual Distortions scores pre- and during the infusion across the placebo and ketamine groups. Bars represent standard errors.

Correlations

The difference in the PSI Perceptual Distortions subscale scores (during the infusion – pre-infusion/baseline; Figure 2.3) tended to positively correlate with direct SP in the strategic condition ($r = 0.44$; $p = 0.012$) in the ketamine groups. There were no other correlations.

Table 2.5 Subjective rating scales: mean (SD) scores across the placebo and ketamine groups pre- and during the infusion and the 3 x 2 Group x Time interactions

	Scores						Analyses	
	Placebo		Low-dose		High-dose		Group x Time	
	Pre-infusion	During	Pre-infusion	During	Pre-infusion	During	$F_{2, 45}$	p
Brief Psychiatric Rating Scale								
Positive Symptoms	4.63 (0.72)*,¶	4.19 (0.54)*,¶	4.69 (0.87)†,¶	4.94 (0.77)†,¶	4.44 (0.63)	6.38 (1.36)	19.25	<0.001
Negative Symptoms	3.00 (0.00)*,§	3.00 (0.00)*,§	3.25 (0.58)†,§	3.63 (1.03)†,§	3.13 (0.34)	4.50 (1.86)	6.33	0.004
Anxious Depression	7.69 (1.45)	6.44 (0.63)	8.31 (1.96)‡,||	6.81 (0.91)‡,||	7.06 (1.44)	7.75 (1.29)	8.43	0.001
Activation	3.13 (0.34)	3.25 (0.45)	3.06 (0.25)	3.06 (0.25)	3.31 (0.60)	3.31 (0.60)		NS
Psychotomimetic States Inventory								
Perceptual Distortions	1.00 (1.90)*,§	1.31 (2.02)*,§	0.56 (0.96)	2.44 (2.48)	1.25 (2.41)	3.94 (3.11)	3.25	0.048
Cognitive Disorganisation	6.50 (4.66)*,||	5.50 (4.78)*,||	4.13 (3.01)	6.25 (4.30)	5.13 (4.47)	9.44 (5.13)	4.78	0.013
Delusory Thinking	2.25 (2.44)	0.94 (1.34)	1.38 (2.00)	1.31 (2.24)	2.13 (2.19)	1.19 (1.68)		NS
Anhedonia	4.69 (2.52)	5.13 (2.71)	4.56 (3.01)	4.63 (2.47)	4.12 (2.16)	5.63 (3.91)		NS
Mania	3.31 (1.54)	3.63 (1.63)	3.00 (1.32)	3.00 (1.71)	3.63 (2.94)	3.44 (1.71)		NS
Paranoia	1.44 (1.46)	0.63 (1.31)	0.69 (1.01)	1.19 (2.29)	0.94 (0.77)	0.56 (0.73)		NS
Total Score	19.19 (10.73)*,§	17.13 (9.93)*,§	14.31 (8.41)	18.81 (10.24)	17.19 (10.33)	24.04 (10.85)	4.76	0.013
Adapted Dissociative States Scale								
Amnesia	0.63 (1.15)*,¶	0.38 (0.81)*,¶	0.31 (0.60)†,§	1.13 (0.96)†,§	0.50 (0.82)	2.19 (1.47)	12.35	<0.001
Depersonalisation	0.63 (1.54)*,§	1.00 (1.93)*,§	0.31 (0.70)†,§	1.38 (1.59)†,§	0.31 (1.02)	4.00 (4.60)	5.58	0.007
Derealisation	2.31 (4.47)*,||	3.38 (4.76)*,||	1.19 (1.72)†,§	3.94 (3.62)†,§	1.63 (3.79)	7.88 (5.06)	7.47	0.002

Total Score	3.56 (6.82)*,||	4.75 (7.11)*,||	1.81 (2.71)†,||	6.44 (5.54)†,||	2.44 (5.38)	14.06 (9.87)	9.59	<0.001
Subjective Effects Scale								
Bodily Symptoms	22.94 (22.71)*,§	43.00 (35.26)*,§	19.75 (35.18)†,¶	121.13 (103.10)†,¶	25.75 (34.57)	212.60 (110.39)	11.98	<0.001
Perceptual Symptoms	12.19 (13.68)*,¶	27.50 (30.24)*,¶	7.31 (9.52)†,¶	67.69 (57.74)†,¶	18.76 (30.35)	218.00 (126.75)	21.55	<0.001
Cognitive Symptoms	23.94 (20.00)*,¶	27.94 (26.99)*,¶	13.94 (21.91)†,||	63.88 (59.35)†,||	21.81 (24.22)	127.62 (71.81)	15.51	<0.001

NS – not significant.

Significant contrasts on change scores (during the infusion – pre-infusion/baseline):

* a significantly greater increase in scores during the infusion in both ketamine groups relative to placebo group;

† a significantly greater increase in scores during the infusion in the high-dose relative to low-dose ketamine group;

‡ a significantly greater decrease in scores during the infusion in the low-dose relative to high-dose ketamine group.

§ $p < 0.05$;

|| $p < 0.01$;

¶ $p \leq 0.001$.

2.4 Discussion

The main finding was that the greater direct SP in the strategic than in the automatic condition, seen in the placebo group, was absent in both of the ketamine groups. Significant direct SP effects, as well as facilitation, and indirect SP were obtained. There was no evidence of inhibition. Explicit measures of semantic memory function did not demonstrate any effects of ketamine administration.

As predicted, both low-dose and high-dose ketamine groups failed to show the expected increased direct SP when the task parameters promoted strategic processing, compared to when processing was restrained to automatic levels. This effect was seen clearly in the placebo group. Although no inverse priming was found with the current paradigm, the results of the current study are not incongruous with Morgan et al.'s (2006b) findings. Both studies found ketamine-induced reductions in direct SP only in conditions that promote strategic processing. This could be an indication of a failure to efficiently use strategic mechanisms, such that ketamine interferes with the generation of expected targets or semantic matching. In contrast, automatic processing was preserved after ketamine administration. The facilitation data overall suggest that the higher SP in the strategic condition compared with SP in the automatic condition was obtained due to increased facilitation in the strategic condition compared with the automatic. However, facilitation data did not mirror the group differences found in direct SP.

No group differences emerged on the indirect SP task, supporting the notion that acute ketamine only affects strategic levels of semantic processing, regardless of whether the words are directly or indirectly related. It is therefore possible that the observed ketamine-induced changes in SP, when strategic processing is promoted, are not specific to semantic memory but are due to more general changes in so-called executive functions. These could include working memory, response inhibition and sustained attention (Donohoe et al., 2006). Indeed, studies have found that ketamine acutely impairs sustained attention (e.g.

Krystal et al., 1994; Malhotra et al., 1996). Impairments in attention have also been found in schizophrenia (e.g. Kairalla et al., 2008) and these impairments have been suggested to underlie some schizophrenia symptoms (Butler & Braff, 1991).

As expected, ketamine induced positive and negative schizophrenia-like symptoms, perceptual distortions and cognitive disorganisation, in addition to strong dissociative effects and altered bodily sensations. This supports the acute ketamine model of psychosis. In contrast to previous studies (e.g. Pomarol-Clotet et al., 2006) that reported prominent ketamine-induced referential ideas similar to delusions, there was no ketamine-induced increase in delusory thinking, as measured by the PSI. The associations between symptom ratings and SP were only at a trend level, which may suggest that symptoms did not reach a high enough threshold to impact semantic processing, using the current ketamine doses. My acute and chronic ketamine (chapter 3) studies employed the same direct SP task. To avoid repetition, acute ketamine findings are further discussed in chapter 3 in regard to *(i)* the acute and chronic ketamine models of schizophrenia (section 3.3.2), and *(ii)* the methodological considerations of the SP task employed (section 3.3.3).

The main limitation of the present study is that the planned target plasma levels of ketamine (100 ng/ml and 200 ng/ml) had to be reduced to 75 ng/ml and 150 ng/ml due to a high dropout rate on 200 ng/ml. The dropout rate was surprising given that we had successfully piloted the 200 ng/ml dose on my supervisors and myself before the start of the study. In addition, the pharmacokinetic model employed was adopted from a research group in Cambridge who have previously used it in their acute ketamine studies. Nevertheless, due to dropouts several adjustments were made to the initial protocol.

First, the cannulae were inserted into participant's forearms before the beginning of the pre-infusion testing, to separate the anxiety participants might experience due to contact with needles, from the anxiety due to expectations related to the drug. Inserting cannulae just before the start of the infusion

seemed to elevate anxiety levels. Second, during the pre-drug testing Hartmann's solution was administered intravenously. This served two purposes: *(i)* participants got used to having an infusion, and *(ii)* it reduced possible faintness that people might experience due to fasting and dehydration. Third, the drug titration was slowed down to 12 minutes to allow a more gradual onset of ketamine effects. These protocol changes along with the decreased plasma targets enabled us to complete the study. A different pharmacokinetic model could be more appropriate for future acute ketamine studies to enable an investigation of the effects of higher doses of ketamine.

The strict participant selection criteria meant that volunteers included in the study had very little or no experience with psychotropic drugs. Although this is necessary for ethical reasons and to avoid interference from other drugs, having participants who are familiar with drug-induced changes could be beneficial. It would reduce the participant's anxiety and the placebo effect, and thus lower the dropout rate. Notably, the participant who took the longest (2.5 hours) to recover after the infusion (and a lot of snacks) was on placebo.

In summary, the current study is the first to investigate the effects of acute ketamine administration on facilitation and inhibition components of direct SP, as well as on indirect SP. A SP effect was successfully obtained in both tasks. The current study found no modulation of direct/indirect SP by ketamine at an automatic level of processing. However, participants were less likely to employ conscious strategies to aid their lexical decision-making when on ketamine. Further studies are required to clarify whether these changes were due to modulation of expectancy or semantic matching. The modulation of implicit processing of word relatedness was not coupled with the modulation of performance on explicit semantic tasks, which was not affected by ketamine. As expected, ketamine had strong dissociative effects and it induced schizophrenia-like symptoms, especially cognitive disorganisation and perceptual distortions.

Chapter 3: Effects of chronic ketamine on semantic priming

To say that a man is made up of certain chemical elements is a satisfactory description only for those who intend to use him as a fertilizer.

Hermann J. Muller

Preliminary research suggests that chronic ketamine administration—seen in those who use it frequently as a recreational substance—may best model chronic symptoms of schizophrenia (for a review see Jentsch & Roth, 1999). In addition to the effects of repeated exposure being more persistent than the effects of acute exposure, there are qualitative differences between them. Repeated administration of N-methyl-D-aspartate (NMDA) receptor antagonists has been associated with emergence of thought disorder, delusions and auditory hallucinations (Allen & Young, 1978); acute administration of ketamine to healthy individuals more often results in visual illusions. In addition, frequent recreational use of ketamine has also been associated with long-lasting impairments in cognitive processing, including semantic memory function (Curran & Monaghan, 2001; Curran & Morgan, 2000). The current rise in ketamine abuse (McCambridge et al., 2007) also warrants full investigation of its potential impact upon semantic memory function.

Preclinical findings also indicate that repeated exposure to NMDA receptor antagonists may provide a better model of chronic schizophrenia than acute administration (for a review see Jentsch & Roth, 1999). Studies with rodents and non-human primates have shown that changes induced by chronic administration of NMDA receptor antagonists are more isomorphic to schizophrenia symptoms as indicated by *(i)* behavioural measures (e.g. cognitive function and social interaction) and *(ii)* changes in metabolism and neurotransmission, especially in prefrontal regions (e.g. Jentsch et al., 1997a; Jentsch et al., 1997b; Sams-Dodd,

1996). The neurotoxic effects of repeated exposure to NMDA receptor antagonists have been observed in animals, resulting in neuronal death in corticolimbic regions and in cognitive deficits (Ellison, 1994; Ellison & Switzer, III, 1993; Fix et al., 1993). These findings support the view that the neurotoxic effects of NMDA receptor hypofunction underlie cognitive dysfunction in schizophrenia (for a review see Olney & Farber, 1995). Although animal models may be able to reflect some aspects of schizophrenia, an obvious limitation of this approach is that it is not possible to model certain symptoms, notably, language-related deficits.

The only previous study (Morgan et al., 2006b) to investigate the effects of chronic ketamine on semantic priming (SP) is described in section 1.3. Briefly, they found longer response times (RTs) for related prime-target word pairs than for unrelated word pairs, referred to as 'inverse' SP, in their chronic ketamine group. This effect was limited to words of low frequency, indicating a possible degradation of the semantic store. However, as inverse SP was found only at a long stimulus onset asynchrony (SOA) and not at a short SOA, it is more likely that strategic processes employed in a SP task were impaired.

In my acute ketamine study (chapter 2), the only behavioural differences found between the placebo and the ketamine groups were on the direct SP task. There was no evidence of ketamine-induced modulation of indirect SP or of performance on explicit semantic tasks. Therefore, the current study aimed to investigate the effects of chronic ketamine administration on direct SP, and its components: facilitation and inhibition, using the same task as in the acute ketamine study. In contrast to Morgan et al.'s (2006b) task which employed short and long SOAs to create 'automatic' and 'strategic' conditions, the current task manipulated both the SOA and the relatedness proportion to distinguish between automatic and strategic processing. Heavy recreational ketamine users were compared with poly-drug users, matched on drug use apart from ketamine, and also to healthy controls who did not use illicit drugs.

A normal SP effect, that is, reduced RTs to related word pairs compared with unrelated words pairs was expected in the poly-drug (Morgan et al., 2006b) and non-drug control groups. Increased SP was expected in the strategic condition compared with the automatic condition (e.g. Lecardeur et al., 2007) in the poly-drug and non-drug control groups, due to increased facilitation and inhibition. Based on Morgan et al. (2006b), I speculated that SP might be selectively reduced in the strategic condition in the ketamine group. If this was the case, I expected that there would be a lack of inhibition of unrelated word pairs in the strategic condition in the ketamine group. In addition, ketamine was expected to abolish the difference in facilitation of related pairs between automatic and strategic conditions.

3.1 Methods and materials

The current study was approved by the UCL Ethics Committee; all participants gave written, witnessed, and informed consent. The entire study was carried out in accordance with the Declaration of Helsinki.

3.1.1 Participants and design

An independent group design was used with three participant groups: ketamine users, poly-drug controls and non-drug controls (Table 3.1). As ketamine users are also 'poly-drug' users, heavy recreational ketamine users (19; 3 female) were compared with poly-drug controls (18; 8 female) who used similar drugs apart from ketamine, and to illicit drug-naïve healthy volunteers i.e. non-drug controls (26; 22 female). Volunteers were recruited via our existing database and snowball sampling (c.f. Solowij et al., 1992); they were 18-29 years old, native English speakers, had no reported mental health problems and were drug-free at the time of testing as verified by urine analysis. Ketamine users were required to have taken the drug at least once a month for at least one year.

3.1.2 Procedure and assessments

All participants completed a detailed drug history questionnaire, Oxford-Liverpool Inventory of Feelings and Experiences questionnaire (O-LIFE; Mason et al., 1995), the Dissociative Experiences Scale questionnaire (DES; Carlson & Putnam, 1993) that measures trait dissociation, and the direct SP task identical to that employed in the acute ketamine study (see section 2.2.4 (i) for details). They also completed the Spot-the-Word test (Baddeley et al., 1993), a measure that correlates highly with the National Adult Reading Test index (Nelson, 1982) of pre-morbid verbal IQ.

3.1.3 Statistical analyses

Accuracy and RT inclusion criteria were identical to those in the acute ketamine study (section 2.2.5). RT criteria led to the exclusion of 3.2% of the total data. There was no effect of SP task version so results were collapsed across versions. To verify that SP, facilitation and inhibition had occurred, separate paired-samples t-tests were performed on participants' mean RTs comparing the relevant word pairs (for SP: related versus unrelated word pairs; for facilitation: related versus neutral pairs; for inhibition: unrelated versus neutral pairs).

If these paired-samples t-test showed significant differences, group differences and possible interactions were further explored. Separate 3 x 2 repeated measures analyses of variance (RMANOVAs) were performed on *(i)* the degree of SP (calculated as $RT_{unrelated} - RT_{related}$), *(ii)* facilitation ($RT_{neutral} - RT_{related}$) and *(iii)* inhibition ($RT_{unrelated} - RT_{neutral}$) with Group (ketamine users, poly-drug controls and non-drug controls) as a between-subject factor and Condition (automatic versus strategic) as a within-subject factor. Accuracy (% of correct trials) was analysed in a 3 x 2 RMANOVA with Group as a between-subject factor and Condition as within-subject factor. Post-hoc Bonferroni-corrected tests were conducted to explore any significant interactions. SP was correlated with O-LIFE

total score/subscales, DES and ketamine use; to minimise Type-I error, the alpha-level for correlations was set to 0.01.

3.2 Results

3.2.1 Demographics

There were no group differences in age, premorbid IQ (Spot-the-Word test), trait schizotypy (O-LIFE total score or subscales) or trait dissociation (Table 3.1). There were differences in gender between the groups (X^2_2 = 21.48; p < 0.001) due to more females in the non-drug control group than in the poly-drug control and ketamine groups. The ketamine group used ketamine frequently (mean: 17.79 ± 11.05 days per month), recently (mean: 3.74 ± 5.10 days since last use) and in high doses (mean: 990.03 ± 849.71 mg per session) for a mean of 3.30 ± 2.92 years.

Table 3.1 Demographic and background variables (mean, SD) for ketamine, poly-drug control and non-drug control groups

	Ketamine users	Poly-drug controls	Non-drug controls
Age	21.00 (2.24)	21.00 (1.03)	20.15 (2.01)
Spot-the-Word score	49.00 (3.11)	48.28 (4.91)	49.50 (3.25)
O-LIFE	16.42 (4.19)	17.17 (6.72)	14.15 (10.16)
DES	19.07 (8.67)	22.68 (15.85)	24.40 (17.66)

O-LIFE – Oxford-Liverpool Inventory of Feelings and Experiences; **DES** – Dissociative Experiences Scale.

Six poly-drug controls had tried ketamine less than 3 times in the past, and had last used it 120.17 ± 133.83 days previously. There were no group differences in alcohol, amphetamine, cannabis or cocaine use (Table 3.2). Compared with the poly-drug control group, the ketamine group used more ecstasy per session ($F_{1, 33}$ = 4.48; p = 0.042). Urine screens confirmed reported recent drug use.

Table 3.2 Self-reported drug use across the ketamine and poly-drug control groups

Drug used		**Ketamine users**	**Poly-drug controls**
Alcohol (19 ketamine users/ 18 poly-drug controls)	*Last use (days)*	1.05 (0.22)	1.11 (0.90)
	Years used	5.63 (3.17)	6.56 (2.26)
	Frequency (days/month)	19.26 (8.80)	16.83 (6.79)
	Amount per session (units)	10.45 (5.20)	8.53 (4.10)
Cannabis (19/ 18)	*Last use (days)*	125.00 (295.89)	77.06 (257.66)
	Years used	4.45 (1.98)	2.81 (2.88)
	Frequency (days/month)	14.53 (11.41)	17.39 (11.22)
	Amount per session (joints)	2.92 (3.04)	2.50 (1.79)
Ecstasy (19/ 16)	*Last use (days)*	124.26 (250.69)	24.38 (23.92)
	Years used	2.70 (2.63)	1.28 (1.24)
	Frequency (days/month)	2.31 (2.26)	1.12 (1.53)*
	Amount per session (mg)	382.0 (252.65)	219.19 (190.85)
Amphetamine (11/ 6)	*Last use (days)*	410.91 (384.03)	281.67 (235.15)
	Years used	1.46 (4.82)	0
	Frequency (days/month)	0.36 (1.21)	0
	Amount per session (mg)	327.27 (257.02)	125.00 (209.17)
Cocaine (16/ 16)	*Last use (days)*	117.94 (213.57)	159.00 (267.54)
	Years used	1.06 (3.34)	0.50 (0.97)
	Frequency (days/month)	0.25 (0.45)	0.77 (1.11)
	Amount per session (mg)	387.50 (457.62)	137.58 (170.72)

* $p < 0.05$

3.2.2 Assessments

3.2.2 (i) Direct semantic priming task

Data from one poly-drug control were excluded from the analysis due to low accuracy. ***Semantic priming effect*** (Table 3.3): a paired-samples t-test showed shorter RTs for related word pairs (mean: 608.12 ± 90.9 ms) than for unrelated word pairs (mean: 626.42 ± 90.95 ms; $t_{61} = -6.38$; $p < 0.001$), confirming SP had

occurred. The 3 x 2 RMANOVA on SP showed main effects of Group ($F_{2, 59}$ = 5.08; p = 0.009) and Condition ($F_{1, 59}$ = 10.00; p = 0.002) the latter reflecting more priming in the strategic condition (mean: 33.11 ± 33.6 ms) than the automatic condition (mean: 14.6 ± 31.74 ms). Main effect of Group remained significant after ecstasy amount per session was added as a covariate ($F_{2, 58}$ = 6.26; p = 0.003). Post-hoc tests exploring group differences showed only a significant difference between the ketamine users and poly-drug controls (p = 0.007), with the ketamine group showing more SP overall (Figure 3.1).

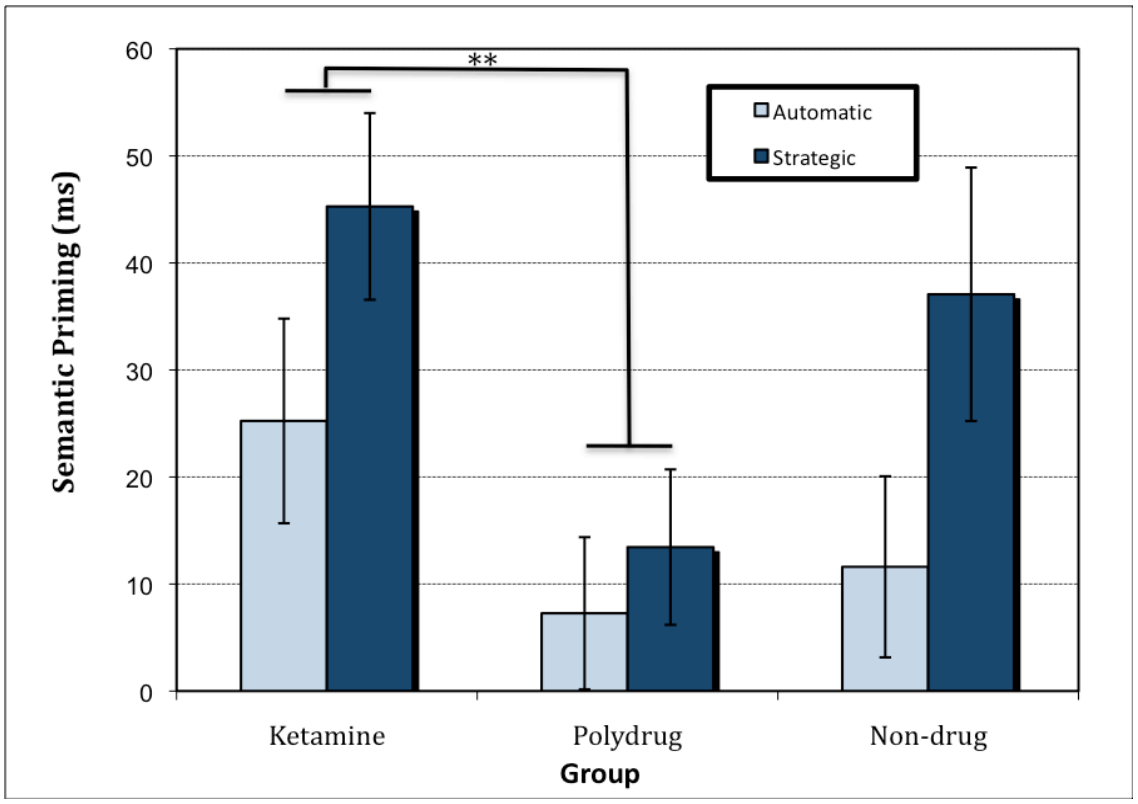


Figure 3.1 Direct semantic priming (RT unrelated - RT related) in the automatic and strategic conditions across the ketamine, poly-drug control and non-drug control groups. Bars represent standard errors.

Facilitation: a paired-samples t-test showed that related pairs were responded to faster than neutral word pairs (mean: 629.78 ± 92.99 ms; t_{61} = -6.99; p < 0.001), confirming that facilitation had occurred. The 3 x 2 RMANOVA showed a trend towards a main effect of Condition ($F_{1, 59}$ = 3.33; p = 0.073), due to more facilitation in the strategic condition (mean: 22.01 ± 36.44 ms) than the automatic condition

(mean: 10.21 ± 35.94 ms). ***Inhibition:*** a paired-samples t-test showed no differences in RTs; therefore, there was no evidence of inhibition. ***Accuracy*** (Table 3.3): the 3 x 2 RMANOVA on accuracy showed main effects of Group ($F_{2, 59} = 4.26$; $p = 0.018$) and Condition ($F_{1, 59} = 15.43$; $p < 0.001$) whereby accuracy was higher in the strategic condition. Post-hoc tests showed that poly-drug controls had lower accuracy than non-drug controls ($p = 0.016$).

Table 3.3 Direct semantic priming task: mean (SD) accuracy and response times across the ketamine, poly-drug control and non-drug control groups

		Ketamine users	Poly-drug controls	Non-drug controls
Accuracy (%)				
Automatic Condition		93.36 (3.76)	92.52 (4.10)	95.16 (2.13)
Strategic Condition		95.03 (2.84)	93.50 (3.71)	95.94 (1.81)
Response times (ms)				
Automatic Condition	*Related*	615.75 (113.89)	616.15 (110.16)	634.36 (80.35)
	Unrelated	640.98 (111.71)	623.42 (103.04)	645.98 (85.83)
	Neutral	627.85 (102.79)	620.86 (109.44)	646.78 (90.12)
Strategic Condition	*Related*	566.30 (91.77)	593.94 (102.62)	610.88 (78.25)
	Unrelated	611.58 (102.61)	607.39 (94.62)	647.95 (82.62)
	Neutral	603.08 (95.08)	608.83 (104.38)	626.75 (82.95)

Correlations

There were trends in the ketamine group towards correlations between SP in the automatic condition and *(i)* the O-LIFE total score ($r = 0.54$; $p = 0.018$), *(ii)* the O-LIFE Unusual Experiences ($r = 0.54$; $p = 0.018$), and *(iii)* the O-LIFE Cognitive Disorganisation ($r = 0.46$; $p = 0.049$).

3.3 Discussion

3.3.1 Effects of chronic ketamine

Chronic ketamine users did not differ in SP from individuals who did not use illicit drugs. Similar to the acute ketamine study, significant SP and facilitation were obtained, and there was no inhibition.

In contrast to acute ketamine, chronic ketamine did not reduce the difference between the automatic and strategic SP. Indeed, although the ketamine group showed increased SP overall compared with the poly-drug control group, this primarily reflected very low priming levels in the poly-drug group. The ketamine group did not differ in SP from the non-drug control group.

One methodological limitation is that the effect seen in the ketamine group could in part be due to concomitant use of other drugs. The ketamine users were all poly-drug users. However, it is unlikely that this could have influenced the results as *(i)* the ketamine users and poly-drug control group were generally well matched on other drug use and *(ii)* the poly-drug control group did not differ from the non-drug control group on SP.

One explanation of this pattern of group differences is that instead of having an additive effect, ketamine might attenuate or reverse some of the effects of other drugs in poly-drug users. A study that examined interactive effects of acute ketamine and amphetamine administration has found that the impairment of working memory produced by ketamine was attenuated by amphetamine (Krystal et al., 2005). The interaction of ketamine and amphetamine could result in a reduction of an impairment caused by one drug, by another, possibly by optimising the level of D_1 receptor function in the prefrontal cortex (Krystal et al., 2005). Since chronic ketamine administration is associated both with the up-

regulation of the NMDA receptor function, as well as the D_1 receptor function, these two mechanisms could have compensatory effects.

In support of this, prefrontal D_1 receptor availability has been found to be up-regulated in chronic ketamine users (Narendran et al., 2005). Therefore, although highly speculative, it is possible that the effect of other drugs—primarily those acting on dopamine (e.g. amphetamine)—seen in the poly-drug control group, has been reversed by repeated exposure to an NMDA receptor antagonist in the chronic ketamine group. This view is supported by the pattern of current SP results. Regional D_1 receptor up-regulation has also been found in schizophrenia (Abi-Dargham et al., 2002), where it might occur as a consequence of NMDA receptor hypofunction.

It is also possible that the differences between the chronic ketamine and the poly-drug control groups in SP might have existed before the onset of drug use. In addition, there could be an interaction of pre-morbid cognitive impairments, with those caused by the drug. There were no group differences on the pre-morbid IQ measure (Spot-the-Word test), however, additional or improved measures might be required to adequately address this issue. For example, a study that assessed pre-morbid cognitive performance based on scores from school tests indicated that poorer cognitive performance might not only be a consequence, but also a predictor of drug use (Block et al., 2002). This hypothesis remains to be tested in frequent ketamine users. Ideally, a prospective study would test children prior to initiation of drug use. These individuals would be tested again as adults, when some of them would presumably go on to using illicit drugs. In contrast to cross-sectional studies, ketamine users could be matched to poly-drug and non-drug controls on performance prior to drug use. A longitudinal study would clarify whether the observed differences between people who use ketamine and other illicit drugs and those who do not are due to pre-existing differences, or are a result of drug use.

The current task did not manipulate word frequencies, and overall the average word frequency was high. Therefore, it was not possible to replicate Morgan et al.'s (2006b) finding that chronic ketamine use resulted in reduced SP for low frequency words in strategic condition. Although Morgan et al. did not demonstrate overall higher SP for high frequency words in ketamine users, there was a tendency for frequency of ketamine use to positively correlate with SP at a short SOA. It is possible that the increased SP for high frequency words was more prominent in the current study due to the fact that the participants were heavier ketamine users compared with the sample tested by Morgan et al.

3.3.2 Do acute and chronic ketamine model schizophrenia?

As the same direct SP task was used in my acute and chronic ketamine studies, it is interesting to compare the pattern of findings in terms of acute and chronic schizophrenia. Reviews of SP studies in schizophrenia (chapter 1; Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007) have established three main factors that contribute to differences between schizophrenia patients and healthy controls. Ketamine-induced SP changes will be considered in relation to these factors; however, as schizophrenia is a highly heterogeneous disorder, all comparisons with findings from schizophrenia research are speculative. For the same reason, comparisons in relation to particular schizophrenia symptoms are more meaningful than comparisons to schizophrenia as a single entity.

A first finding from the reviews is that thought disorder in schizophrenia seems to be associated with increased SP. The only longitudinal study on thought disorder and SP found that this increase is present only while the symptoms persist (Gouzoulis-Mayfrank et al., 2003); in other words, it is state-dependent. Acute ketamine has been shown to induce transient thought disorder (Krystal et al., 1994; Krystal et al., 1998; Malhotra et al., 1996), a finding replicated in the present study (as measured by the PSI Cognitive Disorganisation subscale). Thought disorder symptoms induced by acute ketamine did not correlate with SP in the study reported in chapter 2.

In contrast, there was a tendency for thought disorder (as measured by the O-LIFE Cognitive Disorganisation subscale) to positively correlate with automatic SP in chronic ketamine users; the interpretation of this finding is limited due to the fact that the ketamine users did not show thought disorder on the O-LIFE, and indeed were no different to the control groups. It is possible that the association between SP and ketamine-induced thought disorder would be stronger in chronic users with more pronounced thought disorder. Future studies should investigate the relationship between ketamine-induced thought disorder and SP using a more comprehensive measure of thought disorder, such as the Scale for the Assessment of Thought, Language and Communication (TLC; Andreasen, 1986). Indeed, a detailed comparison of thought disorder induced by acute ketamine in healthy volunteers and in individuals with schizophrenia using TLC found them to be indistinguishable (Adler et al., 1999).

Second, altered SP in schizophrenia is more readily obtained if indirect SP is used, especially at a short SOA. The study reported in chapter 2 was the first study to investigate the acute effects of ketamine on indirect SP. No ketamine-induced changes were observed, although the SOA was short. In addition, there were no correlations between indirect SP and ketamine-induced schizophrenia-like symptoms at the doses studied. The possibility remains that chronic ketamine might have an effect on indirect SP. The indirect SP task was not administered in the chronic ketamine study because it is difficult to engage recreational drug users in lengthy testing sessions. Instead, the direct SP task was chosen, as it seemed more sensitive to the effects of ketamine than the indirect SP task (chapter 2).

The last major finding from the schizophrenia SP literature is that low relatedness proportions are associated with reduced or normal SP in schizophrenia, while higher relatedness proportions result in increased SP. The findings from my acute ketamine study suggest that acute ketamine mirrors these findings only partially. Similar to schizophrenia, there were no changes in SP when the relatedness proportion was low (automatic condition). However, a high relatedness

proportion (strategic condition) resulted in changes that contrasted with schizophrenia findings. Furthermore, chronic ketamine did not have a selective effect on SP in regard to relatedness proportion in automatic or strategic conditions.

Morgan et al. (2006b) did not find any significant correlations between acute ketamine-induced changes in state schizotypy and dissociation with SP. In my acute ketamine study, there was a nearly significant ($p = 0.012$) positive correlation between the strategic SP and state schizotypy subscale (PSI Perceptual Distortions) that corresponds directly with the trait O-LIFE Unusual Experiences. This finding is similar to Morgan et al.'s (2006a) study that investigated differences in SP between healthy individuals with low and high schizotypy scores, and found a tendency for some of the schizotypy traits (as measured by the O-LIFE Unusual Experiences subscale) to correlate with SP when strategic processes are employed (long SOA). In addition, the current study showed there was a tendency for O-LIFE Unusual Experiences to correlate with automatic SP in recreational ketamine users. Taken together with Morgan et al.'s (2006a) study, these findings suggest that both higher trait and state schizotypy characteristics in the perceptual domain may relate to greater SP. The unusual perceptual experiences seem to be related to increased SP even at automatic levels of processing.

It is possible that ketamine has two distinct effects on SP. First, it induces schizophrenia-like symptoms, which seem to result in increased SP. Second, since ketamine impairs executive functions (e.g. attention), it may reduce SP under conditions that promote strategic processing.

3.3.3 Facilitation versus inhibition in semantic priming

Both the current study and the acute ketamine study (chapter 2) set out to investigate ketamine-induced modulation of facilitation and inhibition components of SP. There was no indication of altered SP components after acute or chronic ketamine. However, facilitation and inhibition results should be

interpreted with caution, as the neutral prime pairs did not produce significant RT advantage over the unrelated pairs. There has been much discussion about the choice of a neutral prime (e.g. Chwilla et al., 2000). Studies have employed words *neutral* (Lecardeur et al., 2007), *blank* (de Groot et al., 1982; den Heyer et al., 1986; Kwapil et al., 1990), *context* (Passerieux et al., 1995), *ready* (de Groot et al., 1982), or a string of Xs (de Groot, 1984; den Heyer et al., 1986) as neutral primes. Non-word 'neutral' primes (e.g. *XZXYX*) could require longer encoding times, resulting in longer RTs to neutral pairs and thus overestimation of facilitation. The reverse situation could be created by using a real word repeatedly, due to a reduction in its encoding time (Jonides & Mack, 1984; McNamara, 2005). In addition, the prime could loose its alerting qualities with repetition, leading to overestimation of facilitation (Jonides & Mack, 1984).

With no consensus in the literature on an optimal neutral prime, I chose to use a novel neutral prime: the verb *decide*. The use of this prime does not exclude the possibility of reduced encoding time for the repeated prime. However, it avoids the limitations associated with a non-word prime and, coupled with the instructions, preserves the alerting property of the prime. Therefore, overestimation of facilitation should have been avoided by the current design and it is not clear why significant inhibition was not obtained. In addition, if all neutral primes are coupled with real word targets, the correct answer becomes predictable. The resulting underestimation of facilitation was avoided by including pairs in which neutral primes were followed by non-word targets.

Due to similarities in the task design, it is possible to compare the current pattern of findings to Lecardeur et al.'s (2007) study that investigated direct SP in schizophrenia. They found a trend ($p = 0.053$) for increased SP in schizophrenia, which was due to increased inhibition and was not limited to either the automatic or strategic levels of processing. This was not the case in my acute and chronic ketamine studies. However, having all neutral primes followed by a real word target can lead to a 'real word' bias and thus to overestimation of inhibition; it is

possible that this occurred in Lecardeur et al.'s study. Indeed, they found significant inhibition even at automatic processing levels. This is an unusual result, as inhibition is rarely obtained under automatic conditions. For instance, Neely et al. (1989) did not find any inhibition when a non-word target followed half of the neutral primes. If a neutral word is always followed by a real word and never by a non-word, participants will use this information to speed their response to the target. If this 'real word' bias is a significant contributor towards the inhibition effect, it should not be found in word pronunciation paradigms, where no lexical decision has to be made. For example, Moritz et al. (2002) found shorter RTs to unrelated word pairs than to those containing a neutral prime, when using a string of Xs as a neutral prime in a word pronunciation task.

In summary, acute ketamine induced schizophrenia-like symptoms and dissociation, whereas chronic ketamine users did not show elevated scores on trait schizotypy or dissociative experiences when drug-free. There was no modulation of SP by acute ketamine at an automatic level of processing at the doses studied. However, participants were less likely to employ strategic processing to aid their lexical decision-making when on ketamine. There was a tendency for unusual cognitive and perceptual experiences in ketamine users to be associated with increased SP. Given the above, my findings suggest that the changes in SP induced by acute ketamine and associated with chronic ketamine use may be comparable to some of those observed in schizophrenia.

Chapter 4: Semantic priming in schizophrenia: a behavioural perspective

4.1 Introduction

Semantic priming (SP) studies in schizophrenia were reviewed in detail in section 1.2. To summarise, using a high relatedness proportion in a task, or using indirectly related word pairs with a short stimulus onset asynchrony (SOA), seems to result in more reliable SP differences between people with schizophrenia and healthy controls. In addition, the presence of thought disorder seems to be related to increased SP.

Most of the SP studies in schizophrenia have investigated direct and/or indirect SP, without controlling for basic semantic associative abilities in schizophrenia. At the time when the current study was conducted, only one previous study had administered a SP and explicit semantic processing tasks (e.g. verbal fluency and synonyms) to the same group of schizophrenia patients (Rossell & David, 2006). They found impairment on all semantic tasks in schizophrenia. However, they did not explicitly assess association abilities tapped by direct and indirect SP tasks i.e. whether the direct link was perceived between two words (e.g. *eat* - *food*), or an indirect association (e.g. the word *bee* linking *honey* and *stings*).

Assaf et al. (2006b) explicitly assessed whether schizophrenia patients perceived indirect associations between pairs of words differently to healthy controls. Pairs of words were presented to participants, who had to indicate whether the two words were related to a third, not shown, word. None of the group differences reached significance, however, there were trends for longer response times (RTs) to related pairs, and decreased accuracy due to false positives, in the schizophrenia group relative to healthy controls. In a later study, they developed a task with direct word associations that is equivalent to the initial task with indirect associations (Assaf et al., 2006a). This task has not yet been administered to people with schizophrenia.

The present study aimed to investigate the performance of people with schizophrenia on SP tasks, while also explicitly assessing basic semantic association abilities in the same group of participants. To achieve this, word association strength was manipulated by using directly and indirectly related word pairs. This resulted in four tasks: direct SP, indirect SP, direct explicit association task, and indirect explicit association task. As my review of SP studies in schizophrenia identified a relatedness proportion effect, whereby high relatedness proportions lead to increased SP in schizophrenia, both SP tasks in the current study had a high relatedness proportion. My review was not conclusive in regard to the effect of SOA and so the SP tasks employed both a short and a long SOA.

Based on task parameters, increased direct SP in schizophrenia was expected at both SOAs, as well as increased indirect SP at a short SOA (c.f. chapter 1; Rossell & Stefanovic, 2007). I expected this to be coupled with increased false positives in basic association tasks i.e. decreased accuracy in the non-associated condition in the schizophrenia group compared with healthy controls (Assaf et al., 2006b).

4.2 Methods and materials

This study was approved by the University of Melbourne Human Research Ethics Committee in Australia. Testing of additional healthy volunteers in the UK was approved by the UCL Graduate School Research Ethics Committee. All participants gave written, witnessed, and informed consent. The entire study was carried out in accordance with the Declaration of Helsinki.

4.2.1 Participants and design

Twenty-two schizophrenia patients and 11 healthy volunteers were recruited via a database of participants held at the Mental Health Research Institute of Victoria, Melbourne, Australia. Four additional healthy participants were recruited via a database of participants held at the University College London, London, UK. Six patients met clinical criteria for moderate or severe depression

(Beck Depression Inventory-II (BDI-II; Beck et al., 1996) score > 20) and were excluded from further analysis. One schizophrenia patient was not able to perform the tasks. Data from 15 (11 male) schizophrenia patients and 15 (10 male) healthy controls was included in the final analysis.

Native English speakers were screened by interview and questionnaires to exclude anyone with a history of substance or alcohol misuse, traumatic brain injury, epilepsy, electroconvulsive therapy, or any other neurological or co-existing psychiatric condition (e.g. depression or anxiety). Additional inclusion criteria for the healthy controls were: no current or past psychiatric conditions, and no previous psychotic illness in a first-degree relative. Participants were assessed using the National Adult Reading Test (NART; Nelson, 1982), the BDI-II, the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970) and the 24-item expanded Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986).

All participants in the schizophrenia group were outpatients with chronic symptoms. Diagnosis of schizophrenia patients was confirmed through Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; First et al., 2002). The current psychopathology of the schizophrenia group was rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) on the day of testing. The age of onset and duration of symptoms, medication type and dosage were recorded.

4.2.2 Procedure

All participants completed 2 SP tasks followed by 2 basic association tasks. The administration order of direct and indirect tasks was counterbalanced across the groups.

4.2.3 Assessments

The basic association and SP tasks were programmed using Presentation® software (http://www.neurobs.com). All stimuli were centrally presented.

4.2.3 (i) Basic association tasks

Participants completed the direct and indirect basic association tasks developed by Assaf et al. (2006a). In each task, 32 word pairs were presented, half of which were associated. Word pairs were presented simultaneously for 2700 ms, one word above the other. The response window was set to 3000 ms. In the direct association task participants had to decide whether the two presented words were associated with each other (e.g. *pot - stove*) or not associated (e.g. *pot - car*). In the indirect association task, the associated pairs consisted of words that were features of an object (e.g. *honey* and *stings,* associated with the word *bee*). Word lists are given in appendix E. Participants were instructed to decide whether each presented pair of words was associated with a third word that was not presented.

4.2.3 (ii) Semantic priming tasks

Participants completed 2 SP lexical decision (LD) tasks: one with directly related word pairs and the other with indirectly related word pairs. In each task, the word list contained 180 prime-target pairs: 60 related prime-target pairs, 60 unrelated prime-target pairs and 60 non-word target pairs (relatedness proportion: 33%). The relatedness between two words was determined using the Edinburgh Associative Thesaurus (EAT; Kiss et al., 1973). In the direct SP task, prime and targets in the related pairs were semantically and/or associatively related and had an association value > 10 in the EAT (appendix C). In the indirect SP task, the prime and target words in the related pairs were related through an intermediary word and had association values < 10 in the EAT (appendix D). Non-word targets were taken from the ARC non-word database (Rastle et al., 2002) and were pronounceable, legally spelled sets of letter strings, matched on mean number of letters to real word targets. Each SP task had 4 versions of word lists matched for the mean number of letters, concreteness, imageability and Kucera-Francis word frequency (Kucera & Francis, 1967). The administration of versions was counterbalanced across the groups. Real words were either nouns or verbs.

Half of the words were presented at a short SOA (250 ms) and the other half at a long SOA (750 ms). At both SOAs the prime was presented for 200 ms, followed by a blank screen (50 ms for the short SOA and 550 ms for the long SOA), and finally the target for 200 ms. The response window was set to 2000 ms, after which the next trial was initiated. Participants were asked to decide whether the second word in a pair—the target—was a real word or not, and to respond as quickly and as accurately as possible by pressing the corresponding key ('yes' or 'no').

4.2.4 Statistical analyses

The cut off line for participant exclusion based on high error rates was set to 20% for all of the tasks. Only RTs from correct trials were analysed. For each of the basic association tasks, separate 2 x 2 repeated measures analyses of variance (RMANOVAs) on RTs and accuracy were performed with Group (schizophrenia patients versus healthy controls) as a between-subject factor and Association (associated word pairs versus non-associated word pairs) as a within-subject factor.

For the SP tasks, trials with RTs shorter than 200 ms were excluded from the analyses (c.f. Rossell et al., 2003). This resulted in 0.06% and 0.82% of data being excluded from the direct and indirect SP tasks, respectively. Separate 2 x 2 x 2 RMANOVAs on RTs and accuracy with Group (schizophrenia patients versus healthy controls) as the between-subject factor and Relatedness (related word pairs versus unrelated word pairs) and SOA (short versus long) as the within-subject factors were performed for each SP task.

Patients' current symptoms (PANSS Positive, Negative and General scores), duration of illness (in years) and medication dosage were correlated with the SP effect ($RT_{unrelated} - RT_{related}$) in the schizophrenia group. Medication doses were converted into chlorpromazine equivalents. To reduce Type-I error, the alpha-level for correlations was set to 0.01.

4.3 Results

4.3.1 Demographics

There were no significant group differences in age, years spent in education, NART IQ, BDI-II and trait anxiety scores (Table 4.1). There was a trend for higher state anxiety (t_{28} = 1.75; p = 0.092) in the schizophrenia group compared with the healthy control group. One patient was a cannabis user, however, excluding them from the analysis did not alter the pattern of results and therefore they were included in the final analysis. All patients were medicated (mean chlorpromazine equivalent: 645.73 ± 591.6 mg/day).

Table 4.1 Demographic and background variables (mean, SD) for patients with schizophrenia and healthy controls

	Schizophrenia	**Controls**
Age, years	41.93 (11.65)	38.13 (10.90)
NART score	108.60 (6.51)	113.07 (8.59)
Years spent in education	16.50 (4.43)	16.82 (3.46)
State Anxiety score	35.93 (15.47)	28.00 (8.39)
Trait Anxiety score	35.20 (9.19)	31.60 (8.85)
BDI-II score	7.53 (5.78)	4.27 (4.96)
BPRS total score	-	28.00 (2.04)
PANSS Delusions	2.00 (1.41)	-
PANSS Conceptual Disorganisation	1.50 (1.06)	-
PANSS Hallucinations	2.13 (1.41)	-
PANSS Positive	11.40 (3.89)	-
PANSS Negative	9.80 (4.59)	-
PANSS General	20.93 (4.22)	-
Age at illness onset	23.02 (7.77)	-
Duration of illness, years	18.90 (10.71)	-

NART – National Adult Reading Test; **BDI-II** – Beck Depression Inventory-II; **BPRS** – Brief Psychiatric Rating Scale; **PANSS** – Positive and Negative Syndrome Scale.

4.3.2 Assessments

4.3.2 (i) Basic association tasks

No one was excluded from the direct association task due to low accuracy; however, data from 2 patients were missing. Therefore, the analysis is based on 13 patients and 15 healthy controls. In the indirect association task, 2 participants from each group were excluded due to low accuracy and data from 1 patient were missing; the analysis is based on 12 schizophrenia patients and 13 healthy controls.

Direct association task (Table 4.2): RMANOVA on RTs showed a significant main effect of Group ($F_{1, 26} = 16.56$; $p < 0.001$) whereby RTs were longer for schizophrenia patients (mean: 1775.85 ± 97.64 ms) than controls (mean: 1232.96 ± 90.9 ms). There was also a main effect of Association ($F_{1, 26} = 13.58$; $p = 0.001$) due to RTs in the associated condition (mean: 1390.37 ± 438.51 ms) being shorter than in the non-associated condition (mean: 1579.66 ± 487.49 ms). There were no interactions. RMANOVA on accuracy showed no main effects or interactions.

Table 4.2 Basic association tasks: mean (SD) response times and accuracy across the schizophrenia and healthy control groups

	Response times (ms)		**Accuracy (%)**	
	Schizophrenia	Controls	Schizophrenia	Controls
Direct association task				
Associated	1647.13 (388.89)	1167.84 (356.29)	96.64 (4.85)	97.08 (4.65)
Non-associated	1904.56 (442.16)	1298.08 (328.29)	96.64 (6.05)	97.50 (3.95)
Indirect association task				
Associated	2074.28 (370.77)	1388.47 (303.13)	89.58 (8.14)	87.50 (8.84)
Non-associated	2034.63 (418.10)	1507.93 (324.80)	95.31 (6.59)	96.16 (6.00)

Indirect association task (Table 4.2): There was a significant effect of Group on RTs ($F_{1, 23} = 22.38$; $p < 0.001$) due to longer RTs in the schizophrenia group (mean: 2054.45 ± 92.42 ms) than the healthy controls (mean: 1448.2 ± 88.79 ms). There were no other significant effects or interactions. RMANOVA on

accuracy showed a main effect of Association ($F_{1, 23}$ = 8.26; p = 0.009) due to higher accuracy in the non-associated condition (mean: 95.75 ± 6.18%) than in the associated condition (mean: 88.5 ± 8.4%). There was no main effect of Group or interactions.

4.3.2 (ii) Semantic priming tasks

No participant was excluded due to low accuracy. However, direct SP data for one patient were missing. Therefore, data from 14 schizophrenia patients and 15 healthy controls, and from 15 schizophrenia patients and 15 healthy controls were included in the analysis of the direct and indirect SP tasks, respectively.

Direct semantic priming (Table 4.3): RMANOVA on RTs showed a main effect of Relatedness ($F_{1, 27}$ = 13.98; p = 0.001) whereby RTs to related prime-target pairs (mean: 719.88 ± 25.22 ms) were significantly shorter than to unrelated word pairs (mean: 748.95 ± 26.14 ms), confirming that SP had occurred. There was also a main effect of Group ($F_{1, 27}$ = 7.38; p = 0.011) due to schizophrenia patients having longer RTs (mean: 803.37 ± 36.52 ms) compared with healthy controls (mean: 665.455 ± 35.28 ms), and a main effect of SOA ($F_{1, 27}$ = 4.32; p = 0.047). RTs were shorter at a long SOA (mean: 725.33 ± 24.57 ms) than at a short SOA (mean: 743.49 ± 26.91 ms). There were no significant interactions.

RMANOVA on accuracy showed a main effect of Relatedness ($F_{1, 27}$ = 5.21; p = 0.031) whereby accuracy was higher for related prime-target pairs (mean: 98.27 ± 0.48%) than for unrelated prime-target pairs (mean: 95.88 ± 1.32%). There were no other main effects or interactions.

Table 4.3 Semantic priming tasks: mean (SD) response times and accuracy across the schizophrenia and healthy control groups

Relatedness, SOA	Response times (ms)		Accuracy (%)	
	Schizophrenia	Controls	Schizophrenia	Controls
Direct semantic priming				
Related, Short	800.22 (116.22)	663.29 (170.44)	97.34 (3.56)	98.22 (2.78)
Unrelated, Short	827.52 (108.62)	682.93 (174.22)	95.95 (4.17)	95.11 (9.99)
Related, Long	776.06 (102.29)	639.93 (154.46)	99.29 (1.42)	98.22 (3.53)
Unrelated, Long	809.67 (120.74)	675.67 (157.69)	96.91 (3.32)	95.56 (9.14)
Indirect semantic priming				
Related, Short	839.42 (139.97)	667.45 (129.10)	96.67 (3.78)	98.22 (2.48)
Unrelated, Short	848.60 (123.29)	683.35 (138.17)	96.67 (4.36)	97.78 (3.25)
Related, Long	814.05 (122.63)	658.08 (136.97)	97.56 (3.67)	97.11 (3.96)
Unrelated, Long	810.51 (122.41)	663.30 (147.95)	95.11 (4.52)	97.78 (3.00)

SOA – stimulus onset asynchrony.

Indirect semantic priming (Table 4.3): There was a main effect of Group ($F_{1, 28}$ = 11.8; p = 0.002) due to longer RTs in the schizophrenia group (mean: 828.15 ± 32.95 ms) than in healthy controls (mean: 668.04 ± 32.95 ms) and a main effect of SOA ($F_{1, 28}$ = 8.19; p = 0.008) due to longer RTs at a short SOA (mean: 759.7 ± 23.57 ms) compared with RTs at a long SOA (mean: 736.49 ± 23.73 ms). There was no main effect of Relatedness and no significant interactions. RMANOVA on accuracy showed no main effects or interactions.

Correlations: there were no significant correlations between the SP effect and the patients' symptoms, duration of illness or neuroleptics.

4.4 Discussion

> *I believe that on the whole my schizophrenics were not as schizophrenic as they could have been if I had selected extreme examples.*
>
> Leo E. Hollister (1962, pp. 91)

The current study set out to compare semantic processing by people with schizophrenia with that by healthy volunteers. Processing of semantic relationships was assessed both implicitly, using SP tasks, and explicitly, using basic association tasks. Schizophrenia patients were group-matched to healthy volunteers for basic demographics, including pre-morbid verbal IQ. The only behavioural difference found between the groups on all tasks was that schizophrenia patients were slower to make their responses than healthy volunteers. Surprisingly, there were no differences in accuracy between the groups.

A direct SP effect was successfully obtained on both the RT and the accuracy data: RTs were shorter and accuracy higher for related word pairs than for unrelated word pairs. Although the general pattern of RTs and accuracy between related word pairs and unrelated word pairs in the indirect SP task numerically resembled that of direct SP, the difference between the two conditions did not reach statistical significance. Therefore, no indirect SP was obtained in either of the groups. Possible reasons for the lack of indirect SP are discussed in detail in section 7.1. Nevertheless, there were no group differences on either of the SP tasks despite the predicted increased SP in schizophrenia in *(i)* the direct SP task due to the high relatedness proportion employed, and *(ii)* the indirect SP task at a short SOA (c.f. chapter 1; Rossell & Stefanovic, 2007).

Schizophrenia patients were no less accurate than healthy volunteers at deciding whether a presented string of letters was a real word or not. More importantly, they were as successful as the healthy controls in identifying direct and indirect associations between two words. There was no accuracy advantage or

disadvantage for directly associated word pairs compared with unrelated word pairs in either group on the basic association task. However, accuracy was lower for indirectly associated pairs than for non-associated pairs. Both the schizophrenia patients and the healthy controls failed to perceive the association between some of the indirectly related word pairs.

One of the possible reasons for the negative findings in the current study is that the schizophrenia group predominantly consisted of individuals with low symptomatic profiles. Although they were patients with chronic schizophrenia, their current symptoms were mild. Most importantly, the greatest modulation of SP in schizophrenia in previous studies has been demonstrated in patients with thought disorder (for reviews see chapter 1; Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007). In the current study only 2 patients were experiencing moderate thought disorder at the time of testing, as assessed by the PANSS Conceptual Disorganisation scale; 12 out of 15 exhibited no thought disorder.

A general psychomotor slowing in the schizophrenia group—as indicated by longer RTs on all tasks—is a well-established phenomenon in schizophrenia research (for a review see Morrens et al., 2007). It is found across a variety of tasks (e.g. Brebion et al., 1998; Brebion et al., 2000; Carnahan et al., 1997; Morrens et al., 2008a; Schatz, 1998). It has been proposed that the general slowing in schizophrenia is due to both slowed motor and cognitive processing and that these components may be independent of each other (Morrens et al., 2006). Psychomotor slowing is thought to be an intrinsic feature of schizophrenia, and it seems to be independent from medication (Caligiuri et al., 1993; Henkel et al., 2004), although there are some suggestions that it can be increased or decreased depending on the type of neuroleptic (Henkel et al., 2004; Morrens et al., 2008b; Putzhammer et al., 2004). Psychomotor slowing has been found to be predominantly associated with negative symptoms (Fuller & Jahanshahi, 1999; Henkel et al., 2004; Holthausen et al., 1999; Jogems-Kosterman et al., 2001).

In SP research, it has been argued that longer RTs can lead to increased SP as a result of a psychometric artefact (section 1.2.6). Despite longer RTs in the schizophrenia group, SP was not increased in the current study. In addition, there was no correlation between SP and medication doses or negative symptoms. Therefore, it seems that both implicit and explicit processing of semantic relatedness was genuinely intact in the schizophrenia patients included in this study. It has been argued that modulated SP in schizophrenia is only present during acute psychotic episodes and not when the symptoms resolve (Gouzoulis-Mayfrank et al., 2003). The current findings partially support this view.

My findings contrast with those of Rossell and David (2006), who found that the performance of schizophrenia patients was impaired on both implicit and explicit semantic memory tasks. More recently, Kreher et al. (2009) also administered implicit and explicit tasks that assessed processing of direct and indirect word associations in a group of schizophrenia patients. However, they were primarily interested in the N400 effect, and thus their implicit task design did not allow the measurement of behavioural SP. Nevertheless, their explicit task was similar to the one employed in the current study, although directly and indirectly related word pairs were interspersed within one task. Participants pressed a button to indicate whether the two presented words were unrelated, somewhat related, or highly related. No RT data were reported, however their accuracy data resembles the current findings from the indirect basic association task; both schizophrenia patients and healthy controls were more accurate in ratings of unrelated word pairs than of indirectly related pairs.

In conclusion, the present study aimed to investigate semantic function in patients with schizophrenia and compare it to that in healthy volunteers. For this purpose, two SP tasks and two basic association tasks with an analogous structure were employed. Aside from the general slowing found in schizophrenia patients on all of the tasks, there was no modulation of performance in schizophrenia. This is most probably due to the generally asymptomatic profile of the schizophrenia patients.

Chapter 5: Direct semantic priming and its neural correlates in schizophrenia

> *Many psychiatrists and psychologists…still think in the philosophic premises of the nineteenth-century materialism which assumed that all important psychic phenomena must be rooted in (and caused by) corresponding* physiological*, somatic processes.*
>
> Erich Fromm (1955, pp. 70)

5.1 Introduction

As early as the 4th century BC, the role of the human brain was described as the "seat of mental processes", with its importance in health and illness (Clarke & O'Malley, 1996). Many centuries later we have the technology that takes us a step closer to identifying neurophysiological correlates of 'mental processes', including semantic memory function, in functional magnetic resonance (fMRI). The semantic memory system is thought to contain our concept-based knowledge and meanings of words (Schacter et al., 2000). As reviewed in chapter 1, disturbances of semantic memory have been linked to numerous clinical symptoms, including those considered the hallmarks of schizophrenia, such as delusions (Rossell et al., 1999) and thought disorder (Gouzoulis-Mayfrank et al., 2003).

Previous fMRI studies of semantic priming (SP) in healthy volunteers have shown two different patterns of blood-oxygen-level-dependent (BOLD) responses. First, decreased BOLD responses to related pairs relative to unrelated pairs—also referred to as haemodynamic response suppression—have been reported in the left inferior frontal cortex (e.g. Copland et al., 2007; Giesbrecht et al., 2004; Kotz et al., 2002; Matsumoto et al., 2005; Wheatley et al., 2005) and temporal regions (e.g. Copland et al., 2007; Giesbrecht et al., 2004; Matsumoto et al., 2005; Mummery et al., 1999; Rissman et al., 2003; Rossell et al., 2003). These results have been interpreted as reflecting a reduction in the activation

necessary to process pre-activated target words in related pairs. Second, increased BOLD responses to related word pairs relative to unrelated pairs—haemodynamic response enhancement—have been reported in the left inferior frontal cortex (Copland et al., 2007), temporal (Copland et al., 2007; Kotz et al., 2002) and parietal regions (Kotz et al., 2002; Rossell et al., 2003). These results have been interpreted as reflecting the mechanisms underpinning priming, including attentional processes, particularly at longer stimulus onset asynchronies (SOAs; Copland et al., 2007), which are thought to require greater attentional demands. Indeed, previous work has established that the haemodynamic response is influenced by SOA (Rossell et al., 2003).

Behavioural studies of SP in schizophrenia have produced inconsistent results, which may reflect differences in methodology or participant samples (section 1.2). Neuroimaging studies could potentially clarify why these discrepancies occur. Numerous studies have investigated electrophysiological correlates of SP in schizophrenia (e.g. Condray et al., 1999; Condray et al., 2003; Hokama et al., 2003; Kostova et al., 2003a; Kostova et al., 2003b; Kostova et al., 2005; Koyama et al., 1991; Koyama et al., 1994), especially the N400 effect—reduced N400 amplitude to related word pairs compared with unrelated pairs. The N400 effect has been reported to be reduced in schizophrenia (Condray et al., 1999; Condray et al., 2003; Hokama et al., 2003; Kiang et al., 2008; Kostova et al., 2003a; Kostova et al., 2003b; Kostova et al., 2005; Koyama et al., 1991; Koyama et al., 1994). However, due to the poor anatomical specificity of electrophysiological techniques, it remains unclear where in the brain this abnormal response might be occurring. To date only three studies have investigated SP in schizophrenia using fMRI (Han et al., 2006; Han et al., 2007; Kuperberg et al., 2007), one of which is a case study (Han et al., 2006).

Han et al. (2007) investigated auditory SP in schizophrenia using related pairs with either low or high associative connectivity. They reported a step-wise reduction in the BOLD response in the left inferior and middle to superior temporal cortex with the highest response to unrelated word pairs, followed by pairs with low connectivity, and finally pairs with high connectivity. This

response suppression in both areas was more pronounced in the healthy control group compared with the schizophrenia group. The task design did not allow for the comparison of the behavioural SP effect across groups as participants only responded to non-word pairs. Kuperberg et al. (2007) compared people with schizophrenia to healthy controls using visual direct and indirect SP tasks. The pattern of haemodynamic responses differed between the groups, despite the lack of any behavioural differences. Healthy controls showed response suppression to related word pairs, while schizophrenia patients showed response enhancement to related word pairs, most prominently in the inferior prefrontal and temporal regions.

A recent review of structural and functional neuroimaging studies in schizophrenia showed that the findings are often inconsistent between studies (Keshavan et al., 2008). This might reflect symptom heterogeneity, with samples from different studies having diverse symptom profiles. Previous studies reported associations between SP-related BOLD responses in the inferior frontal and temporal areas and auditory hallucinations (Han et al., 2007) and thought disorder (Han et al., 2007; Kuperberg et al., 2007). However, neither of these studies found a correlation with delusions, an association that has been found in behavioural (Rossell et al., 2000) and electrophysiological (Kiang et al., 2008) studies. Knobel et al. (2008) have recently reviewed studies published on the neurobiology of delusions. They concluded that the circuitry involved in the underlying pathophysiology includes temporal and prefrontal regions (Knobel et al., 2008), which are also implicated in SP in healthy volunteers (e.g. Cardillo et al., 2004; Copland et al., 2007; Sachs et al., 2008).

The present study investigated the neural correlates of SP in patients with schizophrenia with diverse symptom profiles to test the hypothesis that the modulation of the BOLD response during a SP task in schizophrenia is associated with specific symptoms. Task parameters included mid-range and long SOAs, and a high relatedness proportion, and therefore promoted use of strategic processing, such as semantic matching (e.g. Neely & Keefe, 1989) and expectancy (e.g. Becker, 1980). I also attempted to replicate group differences found in two

previous studies using *a priori* defined regions of interest (ROIs) within frontal and temporal cortices (Han et al., 2007; Kuperberg et al., 2007). As the task parameters promoted strategic processing, changes were expected to be more pronounced in areas postulated to be involved in attentional processing in SP i.e. in the prefrontal cortex (Mummery et al., 1999; Rossell et al., 2003). I predicted that within the region showing association between the BOLD response and a specific symptom (e.g. delusions), the schizophrenia patients experiencing that symptom would show a modulated response compared with *(i)* patients without that symptom and *(ii)* healthy controls. More specifically, I expected that the pattern of the BOLD response observed in healthy controls would either be less prominent or reversed in these patients (Han et al., 2007; Kuperberg et al., 2007), reflecting an inefficient use of semantic strategic processing. The symptoms investigated have all been reported as having an association with semantic memory disturbances in schizophrenia: hallucinations (Han et al., 2007), thought disorder (Kuperberg et al., 2007), delusions (Rossell et al., 2000) and negative symptoms (Kuperberg et al., 2008).

5.2 Methods and materials

The study was approved by the University of Melbourne Human Research Ethics Committee, Australia. All participants gave written, witnessed, and informed consent. The entire study was carried out in accordance with the Declaration of Helsinki.

5.2.1 Participants and design

Thirty right-handed males participated in the study: 15 schizophrenia patients and 15 healthy controls (Table 5.2). Participants were recruited thorough an existing database of participants held at the Mental Health Research Institute of Victoria, Melbourne, Australia. Healthy controls were group-matched to patients on age, years spent in education and National Adult Reading Test (NART; Nelson, 1982) scores. Participants were native English speakers with no previous history of alcohol or drug dependence, electroconvulsive therapy, traumatic brain injury, epilepsy, or any other neurological or co-existing psychiatric condition, and they

fitted general MRI inclusion criteria. Healthy controls were assessed on the Brief Psychiatry Rating Scale (BPRS; Lukoff et al., 1986) and were not recruited if they had a first-degree relative diagnosed with either schizophrenia or bipolar disorder. All participants in the schizophrenia group were outpatients with chronic symptoms. Diagnosis was confirmed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; First et al., 2002); current symptoms were rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Data on the age of onset and duration of symptoms, as well as the medication was also collected.

5.2.2 Procedure

Participants attended a session at the Murdoch Childrens Research Institute during which they were assessed on the NART, completed interviews, and scanning sessions. All participants completed two SP tasks during separate scanning sessions: a direct and an indirect SP task. Administration of the order of SP tasks was counterbalanced across groups. This chapter reports on the direct SP task, while indirect SP data are presented in chapter 6. Other tasks were also administered (e.g. affective processing task) but are not reported here.

5.2.3 Assessments

5.2.3 (i) Direct semantic priming task

The SP tasks were programmed using Presentation® software (http://www.neurobs.com). In the direct SP task, each word list contained 180 prime-target word pairs: 60 semantically or associatively related, 60 unrelated and 60 with a non-word target (relatedness proportion: 33%). In addition, 60 "null-event" trials were added to provide a baseline. The task had 4 versions of word lists matched for the mean number of letters, concreteness, imageability and Kucera-Francis word frequency (Kucera & Francis, 1967); administration of versions was counterbalanced across groups. The relatedness between two words was determined using the Edinburgh Associative Thesaurus (EAT; Kiss et al., 1973). Related word pairs had an association value > 10 in the EAT (appendix

C). Real words were nouns or verbs. Non-word targets were taken from the ARC non-word database (Rastle et al., 2002) and were pronounceable, legally spelled sets of letter strings, matched on mean number of letters to real word targets.

Half of all the trials were presented at a mid-range SOA (450 ms) and the other half at a long SOA (950 ms); all stimuli were centrally presented. For both SOAs the presentation of the prime (200 ms) was followed by a blank screen for 250 ms or 750 ms for the mid-range and long SOAs, respectively, and finally the target (200 ms). The response window was 2000 ms, after which the next trial was initiated. There was a random start delay (0-300 ms) for each trial to achieve distributed sampling of the haemodynamic response. Participants were asked to read both words in the pair, decide whether the second word (the target) is a real word and indicate their answer by pressing a corresponding key ('yes' or 'no'), as quickly and as accurately as possible (lexical decision task).

5.2.4 MRI scanning

Participants were scanned using a 3T scanner (Siemens Magnetom TrioTim, Erlangen, Germany) while they performed the SP task. A total of 217 images were acquired (30 axial slices; slice thickness = 4 mm; TE = 50 ms; TR = 3300 ms; flip angle = 90°, field of view = 220 mm; matrix 128 x 128; voxel dimension = 1.7 x 1.7 x 4 mm^3). The first 3 images at the beginning of the session were acquired in the absence of any task to allow for scanner stabilisation, and were discarded prior to analysis. High-resolution structural T1-weighted images (176 slices per slab; slice thickness = 1 mm; TE = 2.15 ms; TR = 1900 ms; field of view = 256 mm; voxel dimension = 1.0 x 1.0 x 1.0 mm^3) were also acquired for anatomical localisation.

5.2.5 Behavioural analyses

All participants had greater than 70% accuracy. Individual trials with incorrect answers and trials with unusually fast responses (< 200 ms) were excluded from the analyses (c.f. Rossell et al., 2003); RT criteria lead to exclusion of 3.6% of total data. To verify that SP had occurred, as well as to explore group differences,

2 x 2 x 2 repeated measures analysis of variance (RMANOVAs) were performed separately on response times (RTs) and accuracy with Group (schizophrenia patients versus healthy controls) as a between-subject factor and Relatedness (related word pairs versus unrelated word pairs) and SOA (mid-range versus long) as within-subject factors. SP effect in ms ($RT_{unrelated} - RT_{related}$) was correlated with the PANSS Delusions, Conceptual Disorganisation (index of thought disorder), Hallucinations and total Negative Symptoms scores. To reduce Type-I error, the alpha-level for correlations was set to 0.01.

5.2.6 fMRI analyses

The fMRI BOLD data was analysed using the general linear model within SPM5 (Wellcome Trust Centre for Neuroimaging, London, England; http://www.fil.ion.ucl.ac.uk/spm) implemented within MATLAB (Mathworks Inc., USA). To correct for head movements, all volumes were realigned to the 4th volume after which the data were spatially normalised to fit the Montreal Neurological Institute (MNI) standard brain template and smoothed using a 8 mm full-width half-maximum Gaussian kernel. High-pass temporal filtering at 1/128 Hz and global intensity normalisation were applied. Serial correlations due to aliased biorhythms and unmodelled neuronal activity were corrected using an autoregressive (AR (1)) model. Any scans during which participants moved more than 2 mm translation or 2° rotation were visually inspected for artefacts and replaced by an average of the previous and subsequent volumes if the image was significantly affected. Data from 3 patients with schizophrenia were excluded due to excessive head movement. Regressors, representing 6 conditions (related, unrelated and non-word at mid-range and long SOAs), were created by convolving the onsets of each trial (duration 200 ms) with canonical haemodynamic response function. Non-word trials were not further analysed. Null trials were implicitly modelled. Single-participant contrast maps over the whole brain were created by contrasting *(i)* related and unrelated prime-target trials and *(ii)* mid-range and long SOA trials. The time and dispersion derivatives and the 6 realignment parameters were also included in the model. These contrast maps were combined at group level through random-effects analysis across all participants using a t-test to identify regions showing significant *(i)*

main effect of Relatedness (related versus unrelated), *(ii)* main effect of SOA (mid-range versus long), *(iii)* Group x Relatedness and *(iv)* Group x SOA interactions. Post-hoc analyses of interactions were conducted using SPSS 12.0.1. The ß values were extracted for clusters where significant group interactions emerged for each participant for the within-group analysis; t-tests were conducted on these ß values to determine the nature of the interaction.

ROIs were defined as 10 mm spheres centred around peak coordinates (Table 5.1) for regions previously reported to be modulated during SP tasks in schizophrenia patients relative to healthy controls (Han et al., 2007; Kuperberg et al., 2007). Group x Relatedness and Group x SOA interactions were conducted within these ROIs.

Table 5.1 Coordinates used in the regions of interest analysis based on Han et al. (2007) and Kuperberg et al. (2007)

Source	**Peak**	**Laterality**	**Stereotaxic coordinates (x, y, z)**		
Han et al.*	Superior temporal gyrus	L	-46	-35	5
	Middle frontal gyrus	L	-52	34	20
Kuperberg et al.	Inferior frontal gyrus	L	-51	25	-12
	Inferior temporal gyrus	L	-43	3	-28
	Middle temporal gyrus	L	-57	-19	-8
	Middle temporal gyrus	L	-51	-35	1
	Inferior temporal gyrus	L	-49	-22	-28
	Intermediate orbital gyrus	R	15	55	-10
	Fusiform gyrus	R	37	-53	-8
	Superior temporal gyrus	R	55	8	-4

L – left; **R** – right. * For consistency, the MNI coordinates reported by Han et al. are transformed into stereotaxic Talairach coordinates.

To reduce the likelihood of Type-I error, the Discussion will focus on the effects surviving family-wise error (FWE) correction for multiple comparisons at $p < 0.05$. FWE correction was performed within *a priori* defined ROIs for interactions with Group, and across the whole brain for the whole brain analyses and correlations with symptoms. However, maxima reaching a $p < 0.001$

(uncorrected) threshold with a minimum cluster size of 5 voxels, identified in whole brain analyses (main effects, interactions and correlations) are also reported. Correlational analyses were conducted within the schizophrenia group between the related versus unrelated prime-target trials contrast and PANSS Delusions, Conceptual Disorganisation, Hallucinations and total Negative Symptoms scores, whereby these were entered as covariates in a regression in separate analyses. All MNI coordinates were matched to the stereotaxic array of Talairach and Tournoux (Talairach & Tournoux, 1988) using a non-linear transform (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

5.3 Results

5.3.1 Demographics

There were no differences in age, years spent in education and NART between the groups (Table 5.2). Fourteen of the 15 patients were medicated (mean chlorpromazine equivalent: 574.57 ± 626.58 mg).

Table 5.2 Demographic and background variables (mean, SD) for patients with schizophrenia and healthy controls

	Schizophrenia	**Controls**
Age, years	43.9 (10.5)	44.7 (14.2)
NART score	104.3 (11.1)	108.1 (10.2)
Years spent in education	14.3 (3.1)	14.3 (3.2)
BPRS total score	-	27.3 (2.6)
PANSS Delusions	3.4 (1.84)	-
PANSS Conceptual Disorganisation	2.6 (1.4)	-
PANSS Hallucinations	2.2 (1.66)	-
PANSS positive	14.9 (5.1)	-
PANSS negative	10.4 (3.2)	-
PANSS general	24.4 (4.6)	-
Age at illness onset	22.7 (6.8)	-
Duration of illness, years	20.3 (10.4)	-

NART – National Adult Reading Test; **BPRS** – Brief Psychiatric Rating Scale; **PANSS** – Positive and Negative Syndrome Scale.

5.3.2 Assessments

5.3.2 (i) Behavioural data

The 2 x 2 x 2 RMANOVA on RTs (Table 5.3) showed a main effect of Relatedness ($F_{1, 28}$ = 18.29; p < 0.001) whereby related word pairs (mean: 1062.96 ± 169.98 ms) were responded to faster than unrelated word pairs (mean: 1091.53 ± 167.48 ms), thus confirming that SP had occurred. There was also a main effect of SOA ($F_{1, 28}$ = 11.99; p = 0.002) whereby RTs at a mid-range SOA (mean: 1062.92 ± 163.56 ms) were faster than RTs at a long SOA (mean: 1091.58 ± 174.71 ms), and a Relatedness x SOA interaction ($F_{1, 28}$ = 5.45; p = 0.027) due to more SP at a mid-range SOA (mean: 41.9 ± 48.64 ms) than at a long SOA (mean: 15.25 ± 47.34 ms). There were no main effects or interactions with Group. The 2 x 2 x 2 RMANOVA on accuracy showed a main effect of Relatedness ($F_{1, 28}$ = 6.88; p = 0.014) whereby accuracy was higher for related word pairs (mean: 96.83 ± 4.45%) than for unrelated pairs (mean: 94.78 ± 6.86%). There were no other effects and no significant correlations.

Table 5.3 Direct semantic priming task: mean (SD) response times and accuracy across the schizophrenia and healthy control groups

Relatedness, SOA	Response times (ms)		Accuracy (%)	
	Schizophrenia	***Controls***	***Schizophrenia***	***Controls***
Related, MR	1071.7 (154.3)	1032.6 (163.4)	96.9 (4.5)	98.1 (3.9)
Unrelated, MR	1114.6 (150.5)	1075.8 (161.3)	93.3 (8.2)	97.4 (3.5)
Related, long	1112.1 (160.1)	1078.6 (182.8)	96.7 (3.3)	98.3 (2.2)
Unrelated, long	1138.6 (144.8)	1083.4 (179.6)	94.7 (8.2)	96.4 (4.0)

SOA – stimulus onset asynchrony; **MR** – mid-range.

5.3.2 (ii) fMRI data

ROI-based analyses showed a Group x Relatedness interaction within the right anterior superior temporal gyrus ROI (x = 54, y = 14, z = -3; T = 4.02; p = 0.023, FWE-corrected). Post-hoc analyses showed that this was due to increased BOLD response for related word pairs relative to unrelated pairs in the control group (p = 0.01) and a reversed pattern of response in the schizophrenia group (p =

0.008). There were no other Group x Relatedness or Group x SOA interactions within *a priori* defined ROIs.

No main effects or interactions remained significant after FWE correction for multiple comparisons at $p < 0.05$ in the whole brain analyses. **Main effect of Relatedness:** Regions showing an increase in the BOLD response (at $p < 0.001$, uncorrected) to related word pairs relative to unrelated pairs, independent of Group, included bilateral postcentral and supramarginal gyri, the right medial superior frontal, left lateral superior frontal (extending to precentral gyrus), the right inferior temporal and fusiform gyri and the left insular gyrus (Table 5.4). The reverse contrast showed increased BOLD response to unrelated relative to related condition in the right lateral superior frontal gyrus, bilateral supramarginal gyri (extending to superior temporal gyrus in the right hemisphere), precuneus, and the right middle temporal gyrus. **Group x Relatedness interaction**: The BOLD response was modulated differently by Relatedness between the schizophrenia and healthy control groups (Table 5.5) in the right anterior cingulate and superior temporal gyri and in the region of the left hypothalamus. The overall pattern of haemodynamic response was reversed in the schizophrenia group relative to the healthy control group.

Main effect of SOA: The haemodynamic response to word pairs was higher at mid-range SOA than at long SOA in the right lateral superior frontal gyrus and bilateral inferior frontal gyri across both Groups (Table 5.6). The reverse contrast showed increased BOLD response for long SOA relative to mid-range SOA in the right medial superior frontal gyrus, bilateral superior temporal and right middle temporal gyri, as well as the left occipital gyri, caudate and insula. **Group x SOA interaction:** The BOLD response was increased at mid-range SOA relative to long SOA in the left posterior cingulate gyrus in the healthy control group; this pattern was reversed in the schizophrenia group (Table 5.7).

Table 5.4 Direct semantic priming task: regions showing a main effect of Relatedness (across both groups) on regional BOLD response

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value
Related > Unrelated						
Inferior temporal gyrus	R	45	-73	-1	31	4.77
Fusiform gyrus	R	39	-67	-7		4.02
Supramarginal and postcentral gyri	R	39	-30	37	84	4.44
Supramarginal and postcentral gyri	R	51	-27	40		4.37
Supramarginal and postcentral gyri	R	48	-30	49		4.01
Superior frontal (lateral) and precentral gyri	L	-30	-9	64	6	4.18
Supramarginal gyrus	L	-54	-27	43	8	3.96
Superior frontal gyrus (medial)	R	3	8	52	6	3.89
Postcentral gyrus	L	-39	-29	60	5	3.86
Insular gyrus	L	-36	17	-3	7	3.75
Unrelated > Related						
Precuneus	R	12	-60	25	93	4.78
Precuneus	R	6	-51	33		4.44
Precuneus	L	-6	-51	33		4.02
Superior temporal gyrus	R	39	-57	28	38	4.50
Supramarginal and superior temporal gyri	R	51	-57	33		3.64
Supramarginal gyrus	L	-51	-54	36	20	4.29

Middle temporal gyrus	R	51	-7	-17	12	4.24
Superior frontal gyrus (lateral)	R	18	34	45	6	3.93

All T values are significant at $p < 0.001$, uncorrected.

Table 5.5 Direct semantic priming task: regions showing a Group x Relatedness interaction and the post-hoc analyses

Region	**Laterality**	**Stereotaxic coordinates (x, y, z)**			**Cluster size**	**T value**	**Controls**	**Schizophrenia**
							Direction, P value	***Direction, P value***
Superior temporal gyrus (planum polare)	R	42	-10	-15	9	4.60 *	*Rel > Un, 0.228*	**Rel < Un, 0.001**
Anterior cingulate gyrus	R	12	26	4	14	4.54 †	Rel < Un, 0.015	Rel > Un, 0.003
Hypothalamus	L	-6	0	-3	19	4.25 *	Rel > Un, 0.009	Rel < Un, 0.004
Superior temporal gyrus (planum polare)	R	54	14	-3	19	4.02 *	Rel > Un, 0.01	Rel < Un, 0.008

All T values are significant at $p < 0.001$, uncorrected.
Post-hoc tests: Italics – $p > 0.05$; Bold – $p \leq 0.001$.
* Related > Unrelated, Controls > Patients.
† Related > Unrelated, Patients > Controls.

Table 5.6 Direct semantic priming task: regions showing a main effect of SOA (across both groups) on regional BOLD response

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value
MR > Long						
Superior frontal gyrus (lateral)	R	9	-6	64	14	4.53
Inferior frontal gyrus (pars opercularis)	L	-48	7	22	8	3.94
Inferior frontal gyrus (pars opercularis/triangularis)	R	54	18	13	14	3.84
Long > MR						
Superior temporal gyrus	L	-39	-32	4	36	5.22
Middle temporal gyrus	R	59	-15	-14	19	4.76
Superior frontal gyrus (medial)	R	6	54	33	14	4.44
Caudate	R	33	-26	-1	21	4.43
Insula	R	39	-32	2		3.93
Superior temporal gyrus	R	51	-62	34	18	4.11
Occipital gyri	L	-12	-83	29	7	3.95
Occipital gyri	L	-21	-81	12	7	3.90
Superior temporal gyrus	R	62	-46	19	7	3.76

SOA – stimulus onset asynchrony; **MR** – mid-range.
All T values are significant at $p < 0.001$, uncorrected.

Table 5.7 Direct semantic priming task: regions showing a Group x SOA interaction and the post-hoc analyses

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value	Controls	Schizophrenia
							Direction, P value	***Direction, P value***
Posterior cingulate gyrus	L	-12	-39	32	7	4.11 *	*MR > Long, 0.134*	**MR < Long, 0.001**
Posterior cingulate gyrus	L	-15	-45	27		3.86 *	MR > Long, 0.004	MR < Long, 0.017

SOA – stimulus onset asynchrony; **MR** – mid-range.
All T values are significant at $p < 0.001$, uncorrected.
Post-hoc tests: Italics – $p > 0.05$; Bold – $p \leq 0.001$.
* Related > Unrelated, Controls > Patients.

Correlations: Only one correlation survived the FWE correction across the whole brain. PANSS Delusions scores correlated strongly with the change in the BOLD response signal to related word pairs relative to unrelated pairs with a peak in the left superior frontal gyrus (x = -12, y = 20, z = 46; T = 11.33; p = 0.013, FWE-corrected; cluster size 193; Figure 5.1a) in the schizophrenia group. Greater Delusions scores were associated with increased BOLD responses to unrelated word pairs relative to related pairs i.e. reduced responses to related pairs relative to unrelated pairs. All participants (n = 6) with a high Delusions score (≥ 4) showed an increase in haemodynamic response to unrelated word pairs relative to related word pairs (Figure 5.1b), while all participants (n = 6) with low Delusions (≤ 2) scores showed a reversed pattern of response at this voxel. In order to investigate the pattern of BOLD response in this region in controls, the correlation contrast was masked with related versus unrelated contrast from the controls group using small volume correction.

This showed that the two areas of BOLD response overlapped in the region extending from the left medial superior cortex to the anterior cingulate (peak coordinates in the healthy control group: x = -9, y = 17, z = 43). Masking the correlation image with the reverse contrast in the control group (unrelated versus related) showed no overlap. To confirm that this correlation was not due to possible demographic differences between participants with low and high Delusions score, age, years spent in education and NART were compared between the groups. There were no differences. There were no correlations with PANSS Conceptual Disorganisation, Hallucinations or Negative Symptoms scores ($p < 0.05$, FWE-corrected).

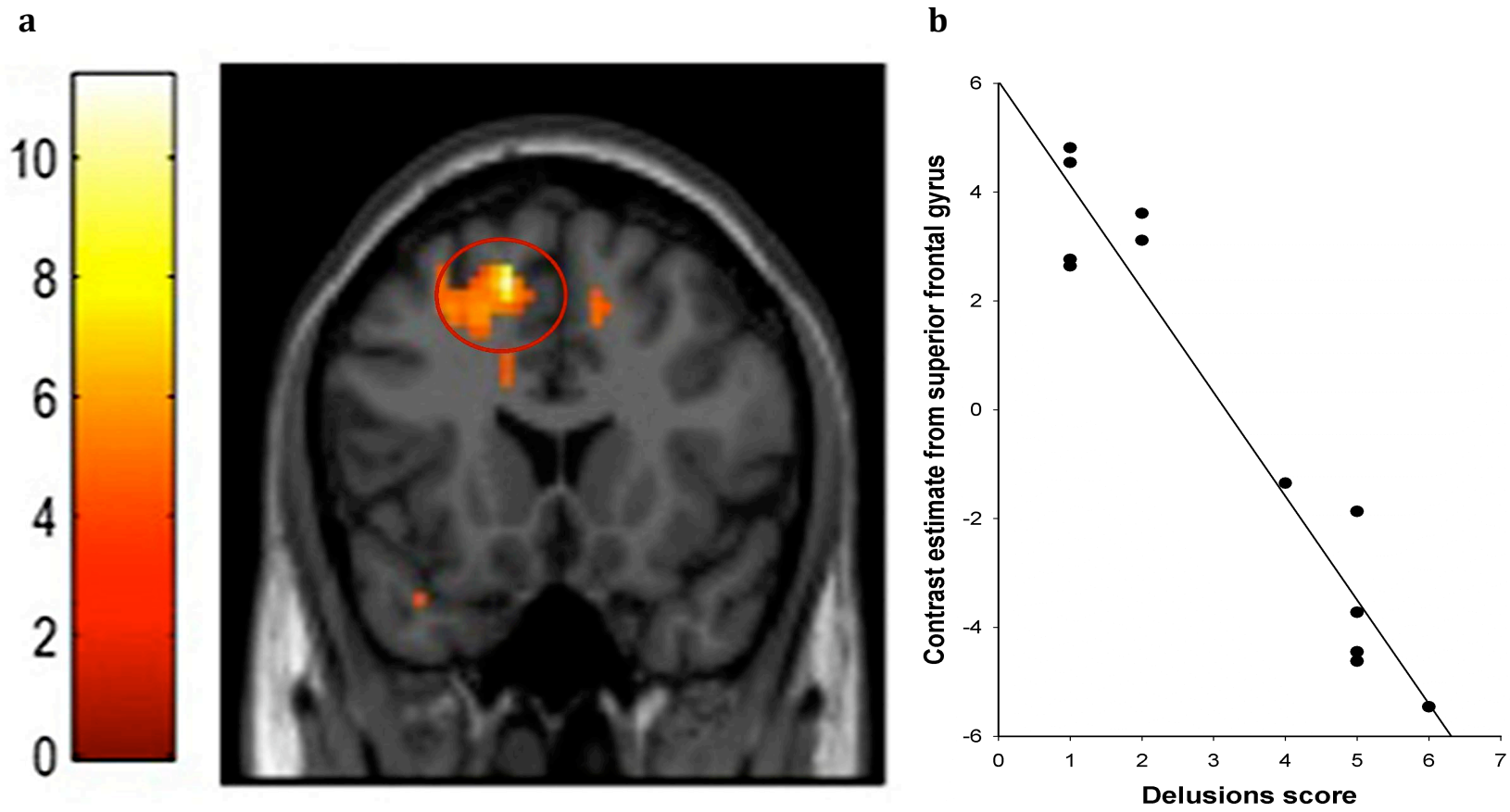


Figure 5.1 Relationship between PANSS Delusions score and the BOLD response to directly related word pairs relative to unrelated word pairs in the schizophrenia group

(a) PANSS Delusions scores were associated with the change in BOLD response to related word pairs relative to unrelated in the left superior frontal gyrus (x = -12, y = 20, z = 46; T = 11.33). This effect was significant at $p < 0.05$, FWE-corrected. T values are indicated by the colour bars; the image was thresholded at $p < 0.001$ for display purposes. **(b)** Correlation between the change in parameter estimates for the related versus unrelated contrast and the PANSS Delusions scores at the peak voxel in the left superior frontal gyrus (r = -0.96).

In addition to the cluster described above, there were other negative correlations ($p < 0.001$, uncorrected) between the PANSS Delusions scores and the BOLD response to related word pairs relative to unrelated pairs (Table 5.8) and no positive correlations. Regions where greater Delusions scores were associated with increased responses to unrelated relative to related pairs (i.e. reduced responses to related pairs relative to unrelated pairs) included the bilateral superior frontal regions and the right inferior temporal gyrus. Greater PANSS Hallucinations scores were also associated with increased responses to unrelated word pairs relative to related pairs (Table 5.9). There were no positive correlations.

Table 5.8 Correlations between the PANSS Delusions scores and regional BOLD responses to directly related word pairs relative to unrelated in the schizophrenia group

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value
Superior frontal gyrus	**L**	**-12**	**20**	**46**	193	**11.33 ***
Middle frontal gyrus	L	-27	11	46		6.79 *
Superior frontal and middle frontal gyri	L	-18	22	38		6.66 *
Superior frontal gyrus (lateral)	L	-18	53	17	14	6.15 *
Superior frontal gyrus (medial)	R	12	16	38	34	6.03 *
Superior frontal gyrus (lateral)	R	21	28	37		4.67 *
Superior frontal gyrus (medial)	R	9	11	49		4.52 *
Superior frontal gyrus (lateral)	R	18	42	28	7	5.78 *
Middle temporal gyrus	L	-56	-53	-7	11	5.73 *
Posterior cingulate gyrus	R	6	-28	26	10	5.57 *
Inferior temporal gyrus	R	45	-50	-8	5	5.36 *
Putamen	R	27	2	47	13	5.36 *
Inferior frontopolar gyrus	L	-12	55	0	16	5.18 *
Orbital gyrus (intermediate)	L	-15	46	-5		4.92 *
Striate area 17	L	-18	-66	12	5	5.08 *

All T values are significant at $p < 0.001$, uncorrected.
Bold – significant at $p < 0.05$, FWE-corrected.
* Negative correlation.

Table 5.9 Correlations between the PANSS Hallucinations scores and regional BOLD responses to directly related word pairs relative to unrelated in the schizophrenia group

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value
Postcentral gyrus	L	-65	-14	20	7	7.72 *
Posterior cingulate gyrus	L	-12	-10	34	42	7.22 *
Superior frontal (medial) and anterior cingulate gyri	L	-12	5	36		6.79 *
Middle frontal gyrus	R	30	-6	47	13	6.74 *
Precentral gyrus	R	36	-18	42		4.54 *
Posterior cingulate gyrus	R	6	-13	31	30	6.03 *
Paracentral lobule and posterior cingulate gyrus	R	12	-12	45		5.86 *
White matter	R	33	-13	28	5	5.96 *
Posterior cingulate gyrus	L	-6	-30	40	30	5.53 *
Paracentral lobule	L	-6	-30	48		4.85 *
White matter	R	3	15	19	12	5.31 *
Superior frontal (medial) and anterior cingulate gyri	R	9	5	44	9	5.21 *
White matter	R	27	-8	22	5	5.00 *

All T values are significant at $p < 0.001$, uncorrected.
* Negative correlation.

Total PANSS Negative Symptoms scores correlated positively with the BOLD response to related pairs relative to unrelated in the middle temporal gyrus (Table 5.10) i.e. greater negative symptoms scores were associated with an increased response to related word pairs relative to unrelated. However, there was also a negative correlation with negative symptoms in the bilateral supramarginal and cingulate gyri, and the right middle temporal gyrus. There were no correlations between the BOLD responses to related word pairs relative to unrelated and the PANSS Conceptual Disorganisation score in the schizophrenia group.

Table 5.10 Correlations between the total PANSS Negative Symptoms scores and regional BOLD responses to directly related word pairs relative to unrelated in the schizophrenia group

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value
White matter	L	-21	-34	27	12	9.00 †
Middle temporal gyrus	R	42	-38	-1	12	6.51 †
Posterior hypothalamic area	L	-3	-12	-2	14	6.43 *
Supramarginal gyrus	R	53	-33	46	17	6.25 *
Posterior cingulate gyrus	M	0	-4	36	23	5.53 *
Anterior cingulate gyrus	L	-6	5	33		5.42 *
Posterior cingulate gyrus	L	-9	-4	33		5.20 *
White matter	R	30	-72	12	5	5.24 †
White matter	R	27	-28	24	6	5.16 †
White matter	L	-9	-22	18	9	5.14 †
Supramarginal gyrus	L	-53	-27	43	5	5.04 *
Postcentral gyrus	R	24	-29	62	7	4.78 *
White matter	L	-12	-31	24	12	4.46 †

All T values are significant at $p < 0.001$, uncorrected.
* Negative correlation; † Positive correlation.

5.4 Discussion

The main finding was that the haemodynamic response to related word pairs relative to unrelated word pairs in the schizophrenia group was strongly associated with the presence or absence of delusions. All schizophrenia patients who had delusions showed a reversed pattern of haemodynamic responses to that of healthy controls. Most importantly, patients without delusions did not. All healthy volunteers and schizophrenia patients without delusions showed response enhancement to related word pairs relative to unrelated word pairs in the left superior frontal gyrus. Conversely, patients with delusions showed response suppression to related pairs. The correlation cluster extended from the lateral to the medial superior frontal gyrus and towards the anterior cingulate ventrally. This pattern of response was also evident in the corresponding region in the right hemisphere, although it was spatially more constrained and it did not reach significance level when the FWE correction was applied.

The current study found differences in the haemodynamic response during a visual SP task between people with schizophrenia and healthy controls in the absence of any behavioural differences. A common limitation of fMRI studies that include people with schizophrenia is that it is not possible to distinguish whether the differences in the BOLD response might be associated with differences in task performance or whether these are independent. The current study circumvented this possible limitation as the groups were well matched on both SP RT effects and accuracy. Lack of behavioural group differences could be due to the fact that only one third of patients in the current study had pronounced thought disorder (as measured by the PANSS Conceptual Disorganisation), as altered behavioural SP in schizophrenia is more readily obtainable in patients with thought disorder (chapter 1; Pomarol-Clotet et al., 2008; Rossell & Stefanovic, 2007).

In line with previous studies (Copland et al., 2007; Rossell et al., 2003), response enhancement to related word pairs relative to unrelated pairs can be interpreted

as a neural correlate of the postlexical meaning integration i.e. strategic employment of semantic matching to facilitate decision making. Long delay between the prime and the target presentation, as well as a high relatedness proportion in the task promoted strategic processing. It is likely that the response enhancement seen in healthy volunteers and patients without delusions reflects semantic strategic processing. Therefore, response suppression to related word pairs found in schizophrenia patients with delusions is indicative of a disrupted employment of conscious strategies in the SP task.

Numerous neuroimaging studies have reported changes in prefrontal responses associated with schizophrenia and/or delusions using a variety of tasks. For instance, Dollfus et al. (2008) found a modulation of the left medial superior frontal gyrus in schizophrenia patients using a language comprehension/theory of mind task; however patients' delusions scores were not reported. Brain degeneration and lesion studies have also implicated prefrontal cortex dysfunction in delusion formation (for a review see Devinsky, 2009). For instance, right prefrontal neurodegeneration is thought to underlie delusion formation in Alzheimer's disease (Sultzer et al., 2003). Another study found an association between high delusion scores and low grey matter density in the left medial frontal gyrus in Alzheimer's (Bruen et al., 2008). In addition to structural changes, functional prefrontal deficits (including the right superior frontal gyrus) have been shown in Alzheimer's patients with delusions in comparison to those without (Nakano et al., 2006). Furthermore, metachromatic leukodystrophy, a disorder that affects prefrontal white matter, can also result in delusional symptoms (Hyde et al., 1992). Last, a recent study (Rossell, Batty and Hughes, submitted) found that a frontal pathology was implicated as underlying delusions in post-traumatic brain injury. All cases in the study had poor semantic memory, including impaired performance on a SP task.

Previous findings have indicated both right and left prefrontal function in association with delusions. A recent review of studies on delusions (Devinsky,

2009) indicates that although the primary pathology underlying delusions seems to be within the right hemisphere, delusions themselves seem to result from the left hemisphere dysfunction (which is caused by the right hemisphere lesion). In other words, a right prefrontal structural change leads to a left prefrontal dysfunction which can in turn result in delusions. My findings support this view, as delusions strongly correlated with the SP-related haemodynamic response in the left superior prefrontal cortex.

Taken together with previous studies, my findings suggest that modulated left prefrontal function could be part of the underlying pathology of delusions in schizophrenia. Furthermore, based on what is known about the function of the prefrontal cortex, this supports the view that delusions might be related to deficits in executive functions, including attention and working memory (Devinsky, 2009; Schultz & Andreasen, 1999). While it is possible that semantic memory deficits play a key role in delusion formation, the neuroanatomical correlates of delusions found in the present study do not provide direct evidence for this notion. A task with a short SOA and a low relatedness proportion that minimizes strategic processing could potentially reveal an association between delusions and 'pure' semantic processing brain areas.

Although the majority of patients were medicated, it is unlikely that the current findings are due to medication effects. First, behavioural studies have found no relationship between performance on SP tasks in schizophrenia and medication (section 1.2.7). Second, altered electrophysiological (section 1.2.11) and haemodynamic (Kuperberg et al., 2007) correlates of SP in schizophrenia seem to be independent from medication. Finally, findings from drug-naïve patients with schizophrenia (Sabri et al., 1997) show an association between delusions and blood flow in the left frontal regions. It therefore seems that the changes in the haemodynamic response pattern in the left prefrontal cortex are specific to delusions in the current patient sample and that they are not related to schizophrenia per se. However, the current study does not distinguish between

different types of delusions. Future studies should investigate whether a similar pattern of haemodynamic response during a SP task that promotes strategic processing would occur in other clinical groups with delusions, for example in delusional disorder.

The current study also attempted to replicate findings from the only two previous fMRI studies on SP in schizophrenia. Similar to Kuperberg et al. (2007) there was a group difference in the response to related pairs relative to unrelated pairs between healthy volunteers and the schizophrenia group in the right anterior superior temporal gyrus. While the two groups showed opposite patterns of haemodynamic response in both studies, the direction of the effect differed between the studies. In the current study there was a response enhancement to related word pairs in healthy volunteers and response suppression in the schizophrenia group; Kuperberg et al. reported a reversed pattern of BOLD response. Copland et al. (2007) also found response enhancement to related word pairs in healthy volunteers, slightly more posterior in the right superior temporal gyrus. The reason for this discrepancy between the studies is not immediately clear, as all three employed tasks with long SOAs. The finding of response enhancement in healthy volunteers is further supported by Rossell et al.'s (2001) study. Using a blocked design, they found a BOLD response in phase with related pairs in the right superior temporal gyrus, although this response was more medial and posterior to ours at a long SOA.

Failure to replicate findings from Han et al. (2007) could be due to methodological differences. For instance, they found group differences in the left posterior superior temporal gyrus. As this region is thought to be involved in speech perception and production (Hickok, 2001) it is not surprising that the difference found using auditory presentation was not replicated using my task with visual presentation.

Many language paradigms have shown differences across gender and with participants of different handedness. As the current study was only able to scan a limited number of participants, to reduce the impact of gender and handedness, only male right-handed individuals were recruited. Although this restricts the generalisability of the results it also increases the power of findings in the current sample.

In conclusion, the current study found a modulation of the BOLD response during a SP task in the left superior frontal region. The reversed pattern of response was related to delusions in the schizophrenia group. Based on previous work, the current study supports the view that delusions are associated with left prefrontal dysfunction and related cognitive deficits involved in semantic processing. The current study also highlights the importance of having a symptoms approach in schizophrenia research as changes in neural function could be related to a specific symptom profile rather than to schizophrenia per se.

Chapter 6: Indirect semantic priming and its neural correlates in schizophrenia

6.1 Introduction

In comparison to direct semantic priming (SP) studies, there are fewer functional magnetic resonance imaging (fMRI) studies that investigated indirect SP. The first study (Tivarus et al., 2006) to investigate blood-oxygen-level-dependent (BOLD) activation during direct and indirect SP in healthy people showed that haemodynamic responses to indirectly related words were less pronounced—although similar—to haemodynamic responses to directly related words. Tivarus et al. found response suppression to directly related word pairs relative to unrelated pairs in the left inferior frontal gyrus, bilateral middle frontal gyri, and bilateral anterior temporal lobes. Weaker response suppression to indirectly related words was found in the left anterior temporal lobe, but not in other areas showing response suppression to directly related pairs.

Tivarus et al. reported no response enhancement to related word pairs relative to unrelated pairs, possibly due to the type of statistical analyses conducted rather than a genuine lack of response enhancement. Specifically, the same dataset was used for the selection of brain regions to be included in the analysis and for the selective analysis, which can result in distorted statistics and invalid statistical inference (Kriegeskorte et al., 2009). Tivarus et al.'s (2006) study employed a long stimulus onset asynchrony (SOA) and found both direct and indirect behavioural SP.

More recently, Sass et al. (2009) employed a SP task with directly and indirectly related word pairs using a short SOA. Their task manipulated the modality (auditory, visual) in which the primes were presented; the targets were always visually presented. This allowed comparisons between ipsi-modal and cross-modal processing of directly and indirectly related word pairs. Their task design

inevitably resulted in a complex pattern of results. There was no effect of modality on behavioural SP; only direct SP was obtained. Ipsi-modal presentation of directly related pairs was associated with haemodynamic response suppression in the right putamen and anterior cingulate and with a widespread response enhancement, mainly in the left fronto-temporal regions. The pattern of haemodynamic responses to indirectly related pairs was predominantly right lateralised: there was response suppression in the prefrontal regions and response enhancement in the right insula and supramarginal gyrus. Cross-modal presentation resulted in fewer regions showing haemodynamic response modulation. Response enhancement was found only for directly related pairs, in the left temporal region. Response suppression to directly and indirectly related pairs was found in the left parietal regions, and left temporal region, respectively.

Only one previous study (Kuperberg et al., 2007) investigated indirect SP in schizophrenia using fMRI. Kuperberg et al. used a long SOA and found no differences in behavioural SP between schizophrenia patients and healthy controls; however, no indirect SP was obtained using their task. Despite the lack of behavioural indirect SP, they found response suppression to indirectly related pairs relative to unrelated pairs in bilateral temporal regions in healthy controls, while the haemodynamic response was reversed in schizophrenia patients.

The present study set out to investigate indirect SP in individuals diagnosed with schizophrenia and healthy controls using fMRI. Based on task parameters, normal behavioural indirect SP was expected in the schizophrenia group (see section 1.2.4). Neuroimaging data, however, were expected to show a reversed BOLD response to indirectly related pairs in the schizophrenia group relative to healthy controls (Kuperberg et al., 2007). As task parameters promoted strategic processing this effect was expected primarily in prefrontal regions, but also in temporal regions (Kuperberg et al., 2007; Tivarus et al., 2006). A replication of group differences found in two previous SP studies in schizophrenia (Han et al.,

2007; Kuperberg et al., 2007) was attempted using *a priori* defined regions of interest (ROIs).

6.2 Methods and materials

The study was approved by the University of Melbourne Human Research Ethics Committee, Australia. All participants gave written, witnessed, and informed consent. The entire study was carried out in accordance with the Declaration of Helsinki.

6.2.1 Participants and procedure

Recruitment, inclusion criteria, participants and procedure are described in section 5.2. Briefly, 30 right-handed males participated in the study: 15 schizophrenia patients and 15 healthy controls. Participants attended a session at the Murdoch Childrens Research Institute in Melbourne, Australia during which they were assessed on the NART, completed interviews, and scanning sessions. All participants completed direct and indirect SP tasks during separate scanning sessions; administration of the order of SP tasks was counterbalanced across groups. Data from the direct SP task are presented in chapter 5; this chapter reports on indirect SP data. The MRI scanning procedure is described in section 5.2.4.

6.2.2 Assessments

6.2.2 (i) Indirect semantic priming task

The structure of the indirect SP task was identical to the direct SP task (see section 5.2.3) with one important difference: in the related pairs, the prime and the target words were indirectly related i.e. they were related through a mediating word (e.g. *rain* - wet - *dry*). Word pairs included as indirectly related pairs (appendix D) had association value < 10 in the Edinburgh Associative Thesaurus (Kiss et al., 1973). The presentation times (450 ms and 950 ms SOAs), the number of trials (60 of

each type: related word pairs, unrelated word pairs, non-word target, and "null-event" trials), the number and administration of versions, as well as participant instructions, were as per the direct SP task.

6.2.3 Statistical analysis

Only data from participants with greater than 70% accuracy were included in the analysis. Individual trials with incorrect answers and trials with unusually fast responses (< 200 ms) were excluded from the analyses (c.f. Rossell et al., 2003); response time (RT) criteria led to exclusion of 2.9% of total data. Behavioural and fMRI data analyses are described in detail in sections 5.2.5 and 5.2.6, respectively.

6.3 Results

6.3.1 Demographics

There were no differences in age, years spent in education and NART between the groups (Table 5.2). Fourteen patients were medicated (mean chlorpromazine equivalent: 574.57 ± 626.58 mg).

6.3.2 Assessments

6.3.2 (i) Behavioural data

Two patients were excluded from the indirect SP task analysis due to low accuracy; in addition, one patient did not complete the task. Therefore, data from 15 healthy controls and 12 schizophrenia patients was analysed. The 2 x 2 x 2 repeated measures analyses of variance (RMANOVA) on RTs (Table 6.1) showed no main effects of Relatedness or Group. However, there was a Group x Relatedness interaction ($F_{1, 25}$ = 9.1; p = 0.006; Figure 6.1). Post-hoc analysis showed that RTs were faster to related word pairs (mean: 1007.81 ± 37.97 ms) than to unrelated word pairs (mean: 1029.67 ± 37.38 ms) in the healthy control group (p = 0.031). In the schizophrenia group, there was a trend for RTs to related

word pairs (mean: 1053.52 ± 42.45 ms) to be longer than RTs to unrelated word pairs (mean: 1032.14 ± 41.79 ms; p = 0.056).

Table 6.1 Indirect semantic priming task: mean (SD) response times and accuracy across the schizophrenia and healthy control groups

Relatedness, SOA	Response times (ms)		Accuracy (%)	
	Schizophrenia	***Controls***	***Schizophrenia***	***Controls***
Related, MR	1042.46 (160.59)	1001.59 (152.21)	95.56 (7.70)	96.00 (4.22)
Unrelated, MR	1028.30 (151.01)	1016.81 (158.06)	92.78 (8.26)	95.78 (3.20)
Related, long	1064.58 (143.49)	1014.04 (139.38)	94.45 (6.41)	95.33 (6.40)
Unrelated, long	1035.98 (119.53)	1042.53 (156.67)	92.50 (9.33)	96.89 (2.95)

SOA – stimulus onset asynchrony; **MR** – mid-range.

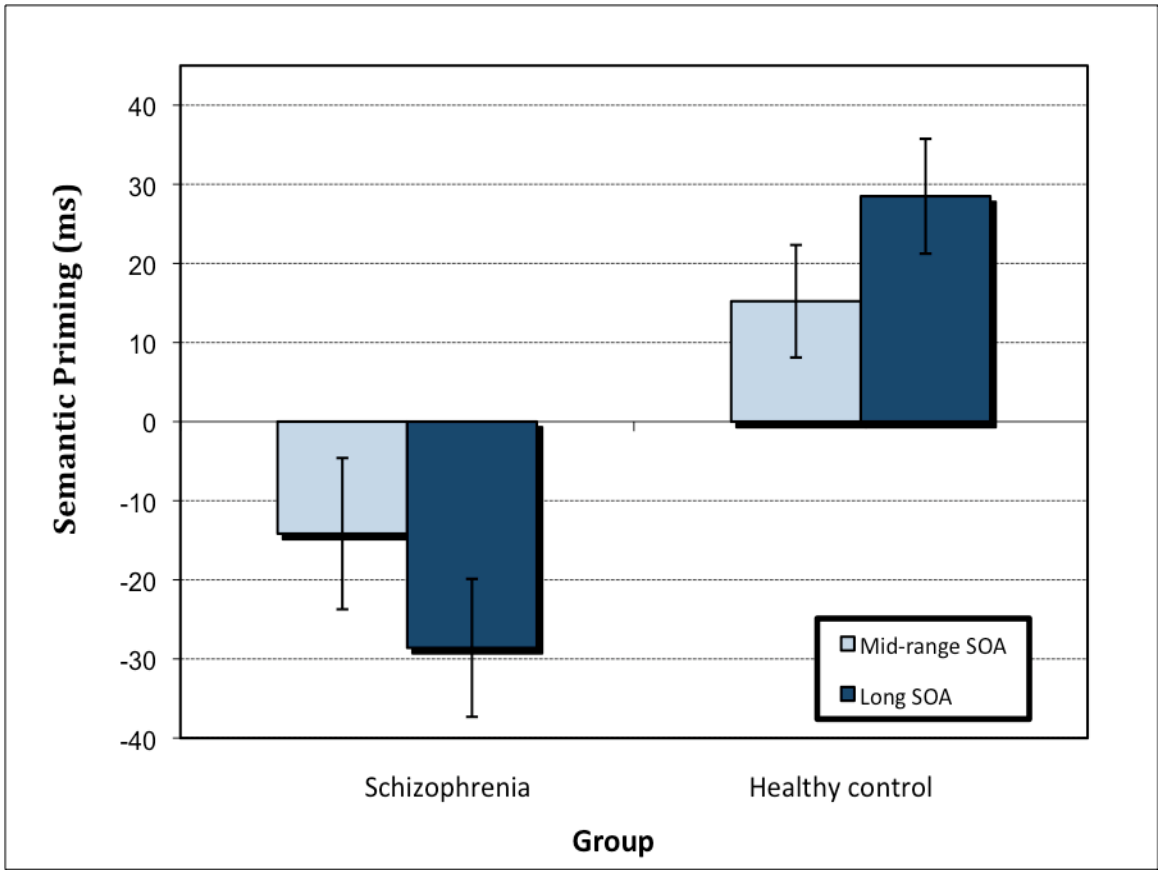


Figure 6.1 Indirect semantic priming (RT unrelated - RT related) across the schizophrenia and healthy control groups at mid-range and long SOAs. Bars represent standard errors.

Therefore, indirect SP had occurred only in the healthy control group. There was also a trend for a main effect of SOA ($F_{1, 25} = 3.68$; $p = 0.066$) whereby RTs were shorter at a mid-range SOA (mean: 1022.29 ± 29.7 ms) than at a long SOA (mean: 1039.28 ± 26.98 ms). Analysis of accuracy yielded no effects. There were no correlations between the SP effect and symptoms in the schizophrenia group.

6.3.2 (ii) fMRI data

Data from 3 schizophrenia patients were excluded from the analysis due to excessive head movement, missing data or low accuracy. Therefore, the results reported are based on data from 15 healthy controls and 12 schizophrenia patients. There were no Group x Relatedness or Group x SOA interactions within the *a priori* defined ROIs and no effects remained significant after family-wise error (FWE) correction for multiple comparisons at $p < 0.05$ in the whole brain analyses. All results reported are significant at $p < 0.001$, uncorrected.

Main effect of Relatedness: There was an increase in the BOLD response to unrelated word pairs relative to related in the left posterior orbital and right lateral superior frontal gyri (Table 6.2). The reverse contrast showed no main effects. **Group x Relatedness interaction:** The BOLD response was lower to related word pairs relative to unrelated pairs in the schizophrenia group in the left inferior frontal gyrus, while there was no effect of Relatedness in the controls group in this region (Table 6.4).

Main effect of SOA: The haemodynamic response was greater at mid-range SOA compared with long SOA, mainly in the right hippocampus, the bilateral precuneus and posterior cingulate gyri (Table 6.3). **Group x SOA interaction:** In the right supramarginal gyrus, schizophrenia patients showed a decreased BOLD response at mid-range SOA relative to long SOA, while the reverse was true for the controls group (Table 6.4).

Table 6.2 Indirect semantic priming task: regions showing a main effect of Relatedness (across both Groups) on regional BOLD response

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value
Unrelated > Related						
Posterior orbital gyrus	L	-27	31	-17	9	4.20
Superior frontal gyrus (lateral)	R	24	54	25	12	4.01

All T values are significant at $p < 0.001$, uncorrected.

Table 6.3 Indirect semantic priming task: regions showing a main effect of SOA (across both Groups) on regional BOLD response

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value
MR > Long						
Hippocampus	R	15	-44	5	56	5.01
Precuneus and posterior cingulate gyrus	L	-3	-49	8		4.48
Precuneus and posterior cingulate gyrus	R	21	-51	36	26	4.17
Superior parietal lobule	R	27	-42	35		4.11
Parietooccipital transition zone	L	-24	-77	26	5	3.82

SOA – stimulus onset asynchrony; **MR** – mid-range.
All T values are significant at $p < 0.001$, uncorrected.

Table 6.4 Indirect semantic priming task: regions showing Group x Relatedness or Group x SOA interactions and the post-hoc analyses

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value	Controls	Schizophrenia
							Direction, P value	*Direction, P value*
Group x Relatedness								
Inferior frontal gyrus	L	-42	25	-16	5	4.28 *	*Rel > Un, 0.428*	**Rel < Un, <0.001**
Group x SOA								
Supramarginal gyrus	R	56	-39	35	10	3.97 †	MR > Long, 0.004	MR < Long, 0.0125

SOA – stimulus onset asynchrony; **MR** – mid-range.
All T values are significant at $p < 0.001$, uncorrected.
Post-hoc tests: Italics – $p > 0.05$; Bold – $p \leq 0.001$.
* Related > Unrelated, Controls > Patients;
† Mid-range > Long, Controls > Patients.

Correlations: The BOLD response to indirectly related relative to unrelated word pairs correlated with PANSS Conceptual Disorganisation positively in the right middle temporal gyrus and negatively in the left superior parietal lobule (Table 6.5). There was a positive correlation with total PANSS Negative Symptoms and the related versus unrelated contrast in the white matter ($x = 18$, $y = -42$, $z = 21$; $T = 4.86$; $p < 0.001$, uncorrected; cluster size = 5). There were no correlations with PANSS Delusions or Hallucinations scores.

Table 6.5 Correlations between the PANSS Conceptual Disorganisation scores and regional BOLD responses to indirectly related word pairs relative to unrelated in the schizophrenia group

Region	Laterality	Stereotaxic coordinates (x, y, z)			Cluster size	T value
Middle temporal gyrus	R	62	-38	-3	5	5.21 †
Superior parietal lobule	L	-27	-52	63	11	5.19 *

All T values are significant at $p < 0.001$, uncorrected.
* Negative correlation; † Positive correlation.

6.4 Discussion

The main finding of the current study is the decreased behavioural indirect SP in patients with schizophrenia compared with healthy volunteers. Significant indirect SP was obtained only in healthy controls. In patients with schizophrenia, RTs to unrelated word pairs were numerically faster than to related pairs, almost reaching significance ($p = 0.056$). In other words, 'inverse' SP (c.f. Morgan et al., 2006b) was obtained in schizophrenia patients. Further, this effect was independent of SOA.

The current study is the first, to my knowledge, to show inverse behavioural indirect SP in schizophrenia. Many studies have shown increased indirect SP in schizophrenia, however, this is most pronounced at short SOAs (e.g. Spitzer et al., 1993a; Spitzer et al., 1993b). Employing longer SOAs previously resulted in normal indirect SP in schizophrenia (Gouzoulis-Mayfrank et al., 2003; Rossell et al., 2000). Longer RTs to indirectly related word pairs relative to unrelated pairs found in the present study are indicative of inhibition of indirectly related word pairs. The current task employed SOAs that promote the use of expectancy. The relatedness proportion was high and this further encourages expectancy, as well as semantic matching. Indirectly related word pairs were presented in the absence of directly related pairs so the participants were more likely to become aware of the association between the indirectly related words (McNamara & Altarriba, 1988). However, indirect associations are less likely to promote strategic processing than direct associations, especially expectancy. Participants are less likely to efficiently predict related targets that will appear to aid their decision-making and therefore unlikely to employ expectancy. Under these conditions, it is more likely that participants would only employ semantic matching to facilitate their responses. Although weak, the association between the prime and the indirectly related target is still perceived and can bias the lexical decision.

It is possible that indirect SP in healthy participants was obtained due to a combination of automatic SP and semantic matching. Speculatively, schizophrenia patients could have tried to employ expectancy i.e. guess which related word would appear as a target. As this is more difficult with indirectly related pairs, incorrect expectations could have led to the inhibition of related targets. Inhibition would also occur for unrelated targets as expectations are violated. However, response to an indirectly related target could further be delayed by the processing of a perceived relationship between the prime and the target. The current results could be interpreted with more certainty if the participants were asked about the strategies they employed. Nevertheless, it is likely that inverse indirect SP in patients with schizophrenia is a result of interference from inefficient employment of conscious strategies.

Compared to the haemodynamic responses obtained using the direct SP task (chapter 5), the effect of word relatedness, as well as the SOA, on the BOLD signal was found in fewer brain regions during the indirect SP task. None of the BOLD signal comparisons survived the FWE correction and there were no significant interactions within the ROIs based on previous studies. However, as many SP fMRI studies report and discuss data that has not been corrected for multiple comparisons across the whole brain (e.g. Copland et al., 2003b; Han et al., 2007; Rossell et al., 2003; Wible et al., 2006), group differences found in the current study using a less conservative threshold will be considered.

Only one region showed a different haemodynamic response to indirectly related pairs in schizophrenia patients compared with healthy controls. Response suppression to indirectly related pairs was found in schizophrenia patients in the left inferior frontal gyrus. Consistent with Tivarus et al. (2006) and Kuperberg et al. (2007), there was no change in the haemodynamic response to indirectly related pairs in this region in healthy volunteers. Left inferior frontal activation during a SP task has previously been found using directly related pairs (Copland et al., 2003b; Kotz et al., 2002; Mummery et al., 1999). The left inferior frontal gyrus

is thought to be involved in the semantic executive system, including semantic aspects of working memory (Bookheimer, 2002; Poldrack et al., 1999). Specifically, its proposed functions include involvement in the retrieval of semantic representations (Demb et al., 1995; Poldrack et al., 1999; Tivarus et al., 2006; Vandenberghe et al., 1996; Wagner et al., 2001), selection between the retrieved representations (Kotz et al., 2002; Poldrack et al., 1999; Thompson-Schill et al., 1997; Thompson-Schill et al., 1999) and evaluation of the chosen information to determine the proper response (Poldrack et al., 1999).

A comprehensive review of neuroimaging studies on semantic processing (Marinkovic, 2004) showed that the same brain area is likely to be involved in multiple stages of word processing. Due to the poor temporal resolution of fMRI, it is not possible to distinguish between different stages of semantic processing. Studies using electroencephalography (EEG) have identified the inferior prefrontal cortex as a part of the network involved in the N400 generation to visually presented words (see section 1.2.11), along with the ventral and anterior temporal regions. Anatomically constrained magnetoencephalographic recordings also support this finding (e.g. Dhond et al., 2003; Marinkovic et al., 2003). Marinkovic et al. (2004) suggest that the N400 and the haemodynamic responses within this network may reflect an attempt to reach semantic and contextual integration as opposed to the actual retrieval of the meaning. In other words, the activation reflects a non-specific engagement of this network. Furthermore, the left inferior frontal cortex and the temporal areas are simultaneously activated during the N400 peak; this has been suggested to represent a sustained interaction between these brain regions in search of meaning (Dale et al., 2000).

fMRI studies of semantic processing focus on distinguishing between distinct roles of brain regions during different stages of semantic processing. It is possible, however, that any information available at any point in time is used in a concurrent manner and that the lexical access and contextual integration occur simultaneously and are inseparable (Marinkovic, 2004). Therefore, it is not

possible to determine which specific subcomponent of semantic processing is impaired in schizophrenia using fMRI. Nevertheless, the abnormal activation of the left inferior frontal gyrus found in schizophrenia patients in the current study indicates an impairment of semantic executive function in schizophrenia. Although speculative, it is possible that the inverse behavioural indirect SP in schizophrenia patients might be related to impaired left inferior prefrontal processing. This view is supported by the fact that both the inverse behavioural SP and the reversed haemodynamic response are most probably due to deficits in conscious, strategic processing of semantic relationships.

In contrast to the direct SP task (chapter 5), there were no highly significant correlations between the current symptoms and the haemodynamic responses in the schizophrenia group. Using a less conservative threshold, greater thought disorder scores (as measured by the PANSS Conceptual Disorganisation) were associated with increased activation to indirectly related word pairs in the right middle temporal gyrus. This region is thought to be involved in the processing of ambiguous information. It shows increased activation during the reading of untitled paragraphs (St George et al., 1999) and during metaphor comprehension relative to sentences with literal meaning (Bottini et al., 1994). In addition, it shows activation when participants are trying to understand semantically anomalous sentences (Kuperberg et al., 2000). It therefore seems that more prominent thought disorder is associated with greater difficulty in perceiving indirect associations.

In conclusion, the current study found an inverse behavioural indirect SP effect in schizophrenia. Healthy volunteers showed indirect SP, while there was inhibition of indirectly related pairs in the schizophrenia group. This was coupled with a modulation of the left inferior prefrontal function. These findings indicate an impairment of strategic processing in schizophrenia during an indirect SP task. The fMRI findings should be interpreted as preliminary as they did not survive the correction for multiple comparisons.

Chapter 7: General discussion

> *The scientific tradition is distinguished from the pre-scientific tradition in having two layers. Like the latter, it passes on its theories; but it also passes on a critical attitude towards them. The theories are passed on, not as dogmas, but rather with the challenge to discuss them and improve upon them.*
>
> Karl R. Popper (2002, pp. 66)

This thesis embodies my investigation of semantic memory processing disturbances in relation to schizophrenia, primarily by employing semantic priming (SP) tasks. My choice of the key paradigm was influenced by the apparent robustness of SP findings in schizophrenia in the previous literature. This chapter begins with an evaluation of the SP paradigm (section 7.1), followed by a consideration of emerging perspectives on SP in schizophrenia (section 7.2), and then a synthesis of my findings in relation to recent research (section 7.3).

7.1 1001 studies later: what do we know about semantic priming?

When I searched for "semantic priming" while writing my final chapter, the search returned 1001 studies, excluding my ketamine study which was already published (ISI Web of Knowledge). Since the discovery of the SP effect, significant progress has been made in regard to methodological fine-tuning and the evolution of theories to account for SP. Importantly, initial simplistic models of SP are being replaced by computational models that can account for a wider range of behavioural findings. Numerous studies have explored the effect of task parameters on promoting or limiting conscious strategies that participants might employ to aid their decision-making, especially expectancy and semantic matching. These indicate that high relatedness proportions and long stimulus onset asynchronies (SOAs) promote strategic processing (section 1.1).

Attempts have been made to distinguish between the components contributing to the SP effect: the facilitation of the processing of the target elicited by related primes and the inhibition from unrelated prime words. However, the search for an ideal baseline to which the effects of related and unrelated primes can be compared continues (see section 3.3.3 for details).

Another enigma in SP research has been the so-called indirect SP. Indirect SP effect is not as robust as direct SP when a lexical decision (LD) task is employed. For instance, Balota and Lorch (1986), and de Groot (1983) failed to find indirect SP. Previous studies suggest that indirect SP is obtained more reliably when the indirectly related pairs are presented in the absence of directly related pairs (Chwilla et al., 2000). This is probably because a *list effect* occurs when the directly and indirectly related pairs are interspersed in one task (McNamara & Altarriba, 1988). That is, the participants start using the most obvious relationships to enhance their performance, thus treating indirectly related pairs as unrelated words. Accordingly, direct and indirect SP effects were explored in separate tasks in my thesis. Despite this, no indirect SP was obtained in my behavioural schizophrenia study (chapter 4) using a task with a high relatedness proportion, and short and long SOAs. In addition, only one group showed indirect SP in my neuroimaging schizophrenia study (chapter 6) using the same relatedness proportion.

The indirect SP task used in my acute ketamine study (chapter 2) was carefully designed in line with previous research which indicated that indirect SP is obtained when task parameters minimise strategic processing (Chwilla et al., 2000; Chwilla & Kolk, 2002). First, a low relatedness proportion was used to avoid expectancy and semantic matching. Second, to further limit the use of expectancy, prime and target words were simultaneously presented (SOA of 0 ms). Last, participants were required to make a word/non-word judgement on both words in the pair (double LD) to limit semantic matching (McNamara & Altarriba, 1988).

An additional important task characteristic, not exclusive to indirect SP, is the position of the presented words on the computer screen. Studies with lateralised presentation show a right visual field advantage: words presented to the right visual field are responded to faster than to the left visual field presentation (section 1.2.5). To avoid the right visual field advantage, both the prime and the target were centrally presented, one above the other. The combination of these task parameters was successful in obtaining indirect SP in my acute ketamine study (chapter 2). This supports the notion that indirect SP is more reliably obtained under automatic conditions, when the use of expectancy and semantic matching is limited.

Indirect SP tasks were initially developed to index the spreading of activation (Spitzer et al., 1993a; Spitzer et al., 1993b) within the semantic memory network from one node to another (section 1.1) as indirect SP was considered a more sensitive measure than direct SP (Spitzer, 1997). Since then, other models have been developed to account for SP effects. McKoon and Ratcliff (1992) were the first to suggest that 'indirect SP' might not be mediated at all, but may simply reflect a weak direct relationship. In their compound cue model (see section 1.1) the 'indirectly' related pairs would have to occur simultaneously in short-term memory during encoding. Out of the more recent models, the composite holographic lexicon model (Jones & Mewhort, 2007) seems to account most effectively for behavioural data including direct SP, 'indirect' SP, 'pure' SP (prime and target words are related only semantically and not associatively), and SP with semantically and associatively related word pairs. Importantly, 'indirect SP' is achieved directly—without any mediators—in this model. It is achieved because two words (e.g. *lion* - *stripes*) share contexts, although to a lesser degree than words that are traditionally thought of as directly related (e.g. *lion* - *tiger*).

In this view, indirect SP is a weaker form of direct SP. This would explain why behavioural indirect SP is less robust than direct SP, and thus has been difficult to obtain in previous studies. In addition to being intuitively appealing, this notion

has been successfully confirmed using computational modelling (Jones & Mewhort, 2007). Neuroimaging studies also support this view. Indirectly related pairs elicit similar electrophysiological (Kreher et al., 2009) and haemodynamic responses (Tivarus et al., 2006) to directly related pairs, however, the response is weaker for indirectly related targets. Therefore, despite extensive research on indirect SP as a separate phenomenon, it seems that the concept of indirect SP might be outdated and should be abandoned.

Considering how much is still unknown about the SP effect it could be argued that the SP paradigm is no longer suitable for exploring impairments in semantic processing, regardless of whether these are endogenous deficits in schizophrenia, or drug-induced. Additionally, SP studies often have statistical power problems given the overall magnitude of the SP effect. However, SP tasks do have some advantages over other semantic memory tasks. First, in contrast to traditional association tests in which the relatedness has to be rated post-hoc for produced associations, in SP tasks word associations are specified in advance. This restricts the range of participants' responses and allows a higher precision in analysis. Second, SP tasks that limit strategic processing are thought to reflect automatic, implicit access to semantic information, as they do not require participants to consciously process semantic relationships between the presented words. Third, and most importantly, SP might pick up subtle differences that are missed by tasks that explicitly assess word association processing. For instance, acute ketamine did not affect verbal fluency tasks or the generation of opposites, whilst it did modulate the SP effect (chapter 2). It is possible that these differential effects reflect, in part at least, differences in task difficulty. An optimal test battery should combine a SP task with various executive function tests as no one task taps into "one process". This would also help to determine whether potential deficits are related so that, for example, the performance on tasks assessing executive function could be covaried with the SP effect.

The order in which the experiments reported in this thesis were actually carried out was: behavioural SP study with schizophrenia patients (chapter 4), neuroimaging of SP in schizophrenia (chapters 5 & 6), followed by the acute ketamine study (chapter 2), and finally, the chronic ketamine study (chapter 3). On reflection, both the direct and indirect SP tasks improved over the course. The tasks used in my ketamine studies have the following advantages. In contrast to my initial direct SP tasks, the improved design distinguished more clearly between automatic and strategic processes by manipulating both the relatedness proportion and the SOA. In addition, my ketamine studies contribute to the discussion on optimal neutral primes by using a novel neutral prime and participant instructions. Finally, as discussed above, after substantial changes to the indirect SP task, my final design successfully obtained indirect SP.

7.2 Semantic priming in schizophrenia: new perspectives

One of the dominant views in SP research is that SP is increased in schizophrenia because activation spreads faster and further within the semantic network, and that this is most pronounced in the presence of thought disorder. Following Manschreck et al. (1988), the idea of increased SP in schizophrenia has been propagated by Spitzer and colleagues (1993a; 1993b; 1994), as well as Moritz and colleagues (2001b; 2001a; 2002), who often adopted the materials and procedures from Spitzer et al. In addition to finding increased direct SP, Spitzer and colleagues (1993a; 1993b) found increased indirect SP in schizophrenia at a short SOA. More specifically, they found indirect SP in schizophrenia patients at short and long SOAs while in healthy volunteers it was evident only at a long SOA (Spitzer et al., 1993a). This led them to conclude that in schizophrenia, the spread of activation through the semantic network is accelerated from one node to another compared with healthy people.

In other words, short SOAs allow enough time for the activation to reach more distant, indirectly related, nodes in schizophrenia, but not in healthy people who show indirect SP only at longer SOAs. This accelerated spread of activation is

thought to lead to intrusions of oblique and unusual associations into a patient's speech because the activity reaches more distant nodes (Spitzer, 1997). Increased indirect SP at short SOAs as a proof for accelerated spreading of activation in schizophrenia is central to Spitzer's theory.

This view faces the following challenges. First, its interpretation is limited to the spreading of activation model. More recent models of semantic memory reject the concept of "indirect SP" as being mediated (see section 7.1). A possibility remains that the retrieval of weakly related word pairs from the holographic lexicon is somehow increased in schizophrenia. Second, numerous studies have found normal or decreased SP in schizophrenia using different procedures to Spitzer and colleagues (see section 1.2). Studies presented in the current thesis also show either normal (chapters 4 & 5) or decreased SP (chapter 6) in schizophrenia.

Third, and most importantly, SP with "indirectly" related words has been repeatedly found in healthy people at short SOAs, using LD and word pronunciation tasks (Balota & Lorch, 1986; Chwilla et al., 2000; McNamara & Altarriba, 1988; Richards & Chiarello, 1995). In my acute ketamine study (chapter 2), indirect SP was successfully obtained in the ketamine groups, and more importantly, in the placebo group using a 0 ms SOA. Indirect SP was also obtained in healthy volunteers in the neuroimaging study at a short SOA (chapter 6).

Even if the overall findings are interpreted within the spreading of activation model, there is still not enough evidence for accelerated spreading of activation in schizophrenia. It is possible that inconsistent results are due to differences in methodology. The majority of studies showing increased SP in schizophrenia (Gouzoulis-Mayfrank et al., 2003; Moritz et al., 2001b; Moritz et al., 2001a; Moritz et al., 2002; Spitzer et al., 1993a; Spitzer et al., 1993b; Spitzer et al., 1994; Weisbrod et al., 1998), or increased SP under dopamine agonists (Kischka et al., 1996; Roesch-Ely et al., 2006) have used materials from the Spitzer group. Other research groups (e.g. Chwilla et al., 2000; McNamara & Altarriba, 1988) show that

indirect SP is more reliably obtained—both in healthy volunteers and in schizophrenia patients—when strategic processing is limited (e.g. at short SOAs, using a low relatedness proportion or a double LD task).

7.3 Semantic priming, schizophrenia and the ketamine model of psychosis

> *If, for instance, one has a toothache, and taking aspirin reduces the pain, one should not jump to the conclusion that the cause of the toothache is too little aspirin in the brain.*
>
> Steven Rose (2005, pp. 234)

The central aim of the studies presented in this thesis was to investigate the modulation of SP and its neural correlates in relation to schizophrenia. My first study (chapter 4) showed no modulation of behavioural direct and indirect SP in schizophrenia, as well as no deficits on explicit semantic memory tasks. The functional magnetic resonance imaging (fMRI) study (chapter 5) also showed a lack of behavioural direct SP differences between people with schizophrenia and healthy controls. The neuroimaging data showed a strong association between delusions and the haemodynamic response modulation in schizophrenia. The pattern of the haemodynamic response in the left superior frontal region during a direct SP task was reversed in schizophrenia patients with delusions compared with both schizophrenia patients without delusions and healthy controls. This modulation of the left prefrontal activation is likely to be associated with executive functions and is not necessarily specific to semantic memory. The neuroimaging study of SP using weakly related word pairs (chapter 6) showed a reversed haemodynamic pattern in the left inferior frontal gyrus in the schizophrenia group compared with healthy controls. This effect was not associated with a particular psychotic symptom. Schizophrenia group showed 'inverse' behavioural indirect SP, and therefore reduced SP compared with healthy controls. These findings indicate that the semantic executive processing in schizophrenia is disrupted.

The main finding from the ketamine studies was the impaired employment of conscious strategies under acute ketamine in healthy volunteers (chapter 2). No differences in SP were found between frequent ketamine users and individuals who do not use illicit drugs; however compared to poly-drug controls, ketamine users showed increased SP (chapter 3). The interpretation of these results is limited due to methodological issues endemic to most studies with illicit drug users. For instance, ketamine and poly-drug users are diverse groups that can include individuals who use drugs recreationally, but also those who might have drug addictions. Nevertheless, recreational ketamine users offer the only window on effects of repeated NMDA receptor antagonist administration in humans, because it is unethical to give ketamine and other NMDA receptor antagonists more than once or twice to volunteers due to their side effects.

To summarise, three key findings indicate that the employment of conscious strategies during semantic processing is impaired *(i)* by ketamine administration to healthy volunteers, and *(ii)* in schizophrenia patients as indicated firstly by behavioural results and *(iii)* secondly by altered prefrontal haemodynamic activation. None of my studies found any modulation of SP when strategic influences were limited i.e. under automatic conditions. The data presented in the current thesis suggest that the disrupted semantic processing in schizophrenia is associated with the so-called executive function impairments and modulated prefrontal function. It is not clear, however, whether or not this impairment is specific to semantic memory processing. Impaired executive functions in schizophrenia have been well described (for a review see Dibben et al., 2009) and have been shown in first-episode drug-naïve patients (Chan et al., 2006), in high risk 'prodromal' individuals prior to their first episode (e.g. Broome et al., 2009; Pukrop et al., 2007), and in non-affected relatives of schizophrenia patients (for a review see Sitskoorn et al., 2004). This suggests that the impairment is not an indirect effect of the illness and is not due to medication. Sustained attention deficits are even considered to be endophenotypic markers for schizophrenia (e.g. Chen & Faraone, 2000).

One of the key aims of my studies was to explore semantic processing deficits in relation to schizophrenia symptoms. As described above, delusions in patients with chronic schizophrenia were associated with modulated prefrontal function. In contrast to previous studies (e.g. Krystal et al., 1994; Krystal et al., 1998; Krystal et al., 2005), acute ketamine did not induce delusions at the doses studied. Chronic ketamine use was also not associated with significant delusions in my study, although increased delusional beliefs in ketamine users have been previously reported (e.g. Morgan et al., 2009a). Therefore it was not possible to explore whether drug-induced delusions in healthy people are associated with semantic processing deficits. An fMRI study employing higher ketamine doses while testing healthy volunteers on a SP task would help clarify whether the reversed prefrontal activation observed in schizophrenia patients with delusions in my study is related to a disruption of glutamatergic transmission. An investigation of neural correlates of SP in recreational ketamine users could further explore whether repeated exposure to NMDA receptor antagonists is a better model of language-related psychotic symptoms.

Acute ketamine induced thought disorder and perceptual changes. My review of previous studies showed that thought disorder might be the best candidate in terms of symptoms associated with impaired semantic function. Acute ketamine-induced thought disorder was not associated with SP. However, in chronic ketamine users there was a tendency for increased SP under automatic conditions to be correlated with thought disorder-like traits. It is possible that this effect may be more pronounced in heavier, daily users with elevated thought disorder-like symptoms. The schizophrenia patients who took part in my studies also did not show prominent thought disorder and there were no correlations between behavioural SP and thought disorder. Interestingly, abnormal temporal and parietal haemodynamic responses to weakly related word pairs were associated with thought disorder (as measured by the Positive and Negative Syndrome Scale) in schizophrenia patients. This indicates an increased difficulty in processing

ambiguous semantic relationships in individuals with thought disorder. Future studies should further explore haemodynamic responses in schizophrenia patients with and without thought disorder during a SP task using either weakly related word pairs or homonym primes.

I proposed that acute ketamine could have a dual action on SP (Chapter 2; Stefanovic et al., 2009). First, it impairs strategic semantic processing which results in decreased SP under strategic conditions. Second, it induces perceptual distortions, which seem to be associated with increased SP. A dichotomy on SP effects has recently been suggested to occur in schizophrenia. Kreher et al. (2009) showed that impaired strategic semantic processing and increased automatic SP, the latter being associated with thought disorder, are not mutually exclusive and can co-occur in schizophrenia. Their task design did not allow behavioural SP comparisons (see section 4.4). However, the electrophysiological data indicated that schizophrenia patients failed to employ a strategic search for semantic relationships during their explicit task. This was reflected in the reduced N400 effect relative to healthy controls. In contrast, increased N400 effect was associated with thought disorder during their implicit task.

Two separate mechanisms with opposing effects on SP could be present in schizophrenia: a deficit associated with psychotic symptoms and altered automatic processing, and executive function impairment associated with strategic SP. This view is suggested by my acute ketamine data. Furthermore, these two mechanisms could act through separate neural pathways. For instance, it has been proposed that positive and negative symptoms in schizophrenia result from dopaminergic function disruption in separate, although related, brain regions. Davis et al. (1991) proposed that decreased prefrontal dopaminergic transmission could be associated with negative symptoms, but could in addition lead to excessive dopaminergic mesolimbic transmission associated with positive symptoms. General executive function deficits and more specific semantic memory impairments associated with positive symptoms in schizophrenia could have

separate underlying neuropathology. Alternatively, specific executive function impairments could be related to particular symptoms and schizophrenia subtypes (Brazo et al., 2002; Donohoe et al., 2006), and could therefore share the underlying neural mechanism.

Schizophrenia symptoms could result from a disrupted glutamatergic regulation of dopaminergic neurons. As discussed in chapter 3, N-methyl-D-aspartate (NMDA) receptor function modulates prefrontal D_1 receptor function. In schizophrenia, NMDA receptor hypofunction is thought to lead to up-regulated prefrontal D_1 receptor availability. This view is supported by neuroimaging studies in schizophrenia (Abi-Dargham et al., 2002) and with chronic ketamine users (Narendran et al., 2005), as well as by combined amphetamine and ketamine challenge studies in healthy volunteers (Krystal et al., 2005). Disrupted NMDA receptor and D_1 receptor function could underlie impairments in working memory, and other executive functions (Krystal et al., 2005).

NMDA receptor hypofunction could also affect subcortical D_2 receptor function, as demonstrated by another study that simultaneously administered ketamine and amphetamine (Kegeles et al., 2000). Amphetamine increases postsynaptic D_2 receptor occupancy, presumably by increasing dopamine, in the striatum. Kegeles et al. showed, using single photon emission computed tomography, that administering ketamine prior to amphetamine to healthy volunteers results in a greater D_2 receptor occupancy. That is, ketamine increases amphetamine-induced dopamine release. Ketamine can also have an effect on dopamine transmission through dopamine transporters, mu opioid receptors and sigma receptors for which it shows some affinity. However, at the doses employed in this thesis and by Kegeles et al. the effect of ketamine is expected to be mediated mainly, if not exclusively, through the NMDA receptors.

Quantitatively, the ketamine-induced enhancement of dopamine release in the striatum (Kegeles et al., 2000) was comparable to the greater response to

amphetamine seen in schizophrenia patients compared with healthy volunteers in other studies (Abi-Dargham et al., 1998; Breier et al., 1997; Laruelle et al., 1996). As suggested by Weinberger (1999), increased amphetamine-induced dopamine release in schizophrenia could result from disrupted glutamatergic regulation of dopaminergic neurons rather than from a primary pathology of these neurons. NMDA receptor dysfunction could therefore lead to positive symptoms, through altering D_2 receptor function.

In summary, my thesis has combined clinical and psychopharmacological approaches to investigate semantic memory in relation to schizophrenia. Acute ketamine findings from healthy volunteers, as well as neuroimaging data from schizophrenia patients indicate that the main impairment in semantic processing could be associated with disturbances in so-called executive functions. These are likely to be a result of altered glutamatergic prefrontal transmission, which in turn disrupts cortical and subcortical dopaminergic transmission. However, no one pharmacological 'model' can begin to encompass the heterogeneous symptoms of the disorder we refer to as schizophrenia. The acute ketamine model has merits in mimicking many acute psychotic symptoms including positive, negative and cognitive symptoms. There is some indication that repeated administration of ketamine could model chronic psychotic symptoms.

The major outcome of pharmacological models of psychosis is ultimately to suggest new treatments. While work for this thesis was being carried out, a successful drug trial was reported (Patil et al., 2007) using a new glutamatergic compound in patients with a diagnosis of schizophrenia. The new compound significantly reduced both positive and negative symptoms without inducing side-effects associated with prolonged use of antipsychotics (extrapyramidal symptoms, prolactin elevation or weight gain). Although this study only investigated short-term effects of a glutamate receptor agonist, it is a step in a new direction for treatment of psychosis.

Finally, several related issues are beyond the scope of my thesis, but are paramount to schizophrenia research. First, increased consensus on, and reliability of, diagnosis would contribute to our understanding, and more precise definition of what we call schizophrenia. Second, a symptoms-orientated approach could prove to be more meaningful and useful than classifying patients into diagnostic categories that often overlap. Third, future research should lead to improved personalised treatments that take into account the heterogeneity of 'schizophrenias'. Last, we need to clearly differentiate between treatments that address the cause of a disorder, and those that alleviate the symptoms. Development of new imaging technologies and further understanding of the existing ones could significantly advance our understanding of schizophrenia.

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