A longitudinal investigation into the influence of atypical antipsychotics on cognitive function in schizophrenia

being a Thesis submitted for the Degree of Doctorate in Philosophy in the University of Hull by Philip John Tyson B.Sc., M.Sc.

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Abstract

Cognitive deficits are a well recognised feature of schizophrenia, with patients showing disproportionate impairments in aspects of memory and executive function. Atypical antipsychotics have shown some success at remediating these deficits which suggests that the basis of the cognitive impairment might be neurochemical in origin. However, the precise nature of this effect is unknown. Mechanisms of action might involve antagonism of 5HT-2A receptors which results in increased prefrontal dopamine, or the affinity of these medications to dopamine receptors or multiple receptors.

Patients with a diagnosis of schizophrenia were recruited for the study within 6 weeks of starting one of the atypical antipsychotics; clozapine, olanzapine, risperidone, quetiapine & amisulpride. They were assessed on clinical variables and a wide battery of cognitive tests at baseline, 9-month-follow-up and 18-month-follow-up. For the analysis the whole group was split into different subgroups according to the neurochemical properties of the individual antipsychotics;

- Those with a high affinity for 5HT-2A receptors (risperidone, olanzapine & clozapine) vs. those with a low affinity for these receptors (quetiapine & amisulpride).
- Those with a preferential affinity for dopamine receptors (risperidone & amisulpride) vs. those with an affinity for multiple receptors (olanzapine, clozapine & quetiapine).
- Those with a fast dissociation from the D2 receptor (clozapine, quetiapine & amisulpride) vs. those with a slower dissociation from this receptor (olanzapine & risperidone)
- In addition the individual medication groups were compared on all measures

The main findings were that medications that had a high affinity for 5-HT2A receptors exerted negative effects on some aspects of cognition, whilst those with a low affinity for 5HT-2A receptors exerted beneficial effects. In addition, the individual atypical antipsychotics differed in their cognitive effects. It is concluded that affinity to 5HT-2A receptors is an important determinant of the cognitive response to atypical antipsychotics.
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Chapter 1: Schizophrenia, cognition and atypical antipsychotics

1.1 What is schizophrenia?

Schizophrenia is a severe psychiatric disorder which is present in all cultures and has an incidence rate of 2 to 4 people for every 10,000 per year (Jablensky et al, 1992). The lifetime risk of developing this disorder is approximately 1%, a figure which is consistent across cultures and suggests that the disorder has a strong biological basis. Some studies have reported a higher risk of developing the disorder in men compared to women (Hagnell et al. 1994), although other research has suggested an equal predisposition between the sexes (Jablensky et al, 1992). However, there are gender differences in the epidemiology of the disorder with men developing the disorder approximately 5 years earlier than women (Hafner et al. 1994). Indeed, the peak incidence of onset is between the ages of 15-25 years in men and 25–35 years in women (Hafner et al. 1994).

The clinical presentation of schizophrenia varies widely between individuals, and within the same individuals across time. However, there are a number of symptoms which are characteristic of the disorder.

1) *Abnormal thoughts*. These often take the form of delusions (false beliefs) which are based on a mistaken inference about reality. The main types of delusions include; persecution—a patient may feel that they are being harassed or persecuted; ideas of reference—a patient may think that events or the behaviour of other people has direct relevance to them; delusions of control—a patient may believe that their thought process or behaviour are being controlled by external forces.
2) *Problems with thought processes and speech.* These types of problems are usually inferred from the spoken or written language of patients which displays abnormalities. The main types are; loosening of associations – speech can become incoherent or difficult to understand because the logical association between ideas is loosened; poverty of speech content – speech is repetitive, stereotyped or vague; thought block – train of thought is suddenly disrupted; neologisms – the patient invents new words or phrases.

3) *Abnormal perception.* This usually takes the form of auditory hallucinations (hearing voices), although visual, olfactory, tactile and gustatory hallucinations can occur.

Auditory hallucinations are represented in a number of ways; voices can speak to the patient directly, they can discuss the patient, they can comment on the patient’s behaviour or they can repeat the thoughts of the patient.

4) *Abnormal affect.* There are two main types of abnormal affect which are usually observed in schizophrenia. Firstly, the patient may demonstrate flat affect, where they have a reduction in the intensity of emotional expression. Secondly, they may demonstrate inappropriate affect where the emotional expression is incongruent with the social situation. Depression is also observed in some patients.

5) *Passivity phenomena.* These refer to symptoms whereby much of a patients internal and external experiences are perceived as not being under their own control, hence the patient is ‘passive’. There are several distinct types of passivity phenomena; thought broadcasting – a patient’s thoughts are broadcast to the outside world; thought insertion – other people’s thoughts are placed in the mind of the patient; thought withdrawal – a patient’s own thoughts are extracted from their mind; made feelings – a patient’s feelings are imposed from an external force; made actions – a patient’s behaviour is under the control of an external agency.
6) **Motor abnormalities.** There are a number of different movement abnormalities that are sometimes observed in schizophrenia; posturing – the adoption of bizarre positions for prolonged periods of time; waxy flexibility – the patient’s limbs become fixed in the position they are placed; negativism – involuntary resistance to attempts at movement; echopraxia – involuntary mimicking of another person’s movements; stereotypy – simple repetitive behaviour; catatonic excitement – intense activity that is purposeless and disorganised; catatonic stupor – lack of movement and inability to interact with the surroundings.

7) **Lack of volition.** Patients often show a lack of interest in themselves or the outside world.

8) **Lack of insight.** Most patients with schizophrenia have either a complete, or partial, lack of awareness of their mental condition.

9) **Cognitive deficits.** Problems with memory, attention and executive function are now a well recognised feature of schizophrenia. These will be discussed in the next section of this thesis.

The time course of schizophrenia is considered to start in childhood where subtle problems with motor skills, linguistic abilities, and social function have been reported (Jones et al. 1994). Following this premorbid stage, there is a prodromal phase which is typified by a decline in functional abilities and the development of ‘positive’ problems such as eccentricity, odd ideas, inappropriate affect and strange perceptual experiences.

After the onset of the full-blown disorder the course of the illness is variable. Indeed, research by Shepherd et al. (1989) suggested that the course of the disorder seemed to follow one of four broad patterns. The first pattern is represented by about 22% of patients who have only one episode of the illness and no long term deficits. The second pattern is typified by
about 35% of patients who experience several episodes of the disorder but have few long term problems. The third pattern comprises about 8% of patients who experience a long term impairment in mental health after the first episode and never return to normality. The fourth pattern is represented by about 35% of patients who experience several episodes of the disorder and become increasingly ill with each subsequent episode.

Although it is impossible on an individual basis to predict the long term outcome for a patient who experiences the first onset of the disorder, a number of factors are associated with better outcome. In terms of socio-demographic features, married patients tend to fare better than single patients, and female patients have better outcome than male patients. Premorbid factors which have a better outcome include; no previous history of psychiatric problems, no pre-existing personality problems, a strong background in education and work, and having good social contacts. Clinically, the features which suggest better outcome include; being older at onset, having an acute onset, having a short episode, starting antipsychotic treatment soon after onset and continuing throughout the episode, having no enlargement of ventricles or widening of sulcal, and having unimpaired neuropsychological functioning (Frangou & Murray, 2000).

Unfortunately, the life span of patients with schizophrenia is shortened by about 10 years in men and 9 years in women (Ohmori et al. 1999). In addition, approximately 10% of patients commit suicide (Heila et al. 1997), and deaths from other causes are also increased, which include accidents and cardiovascular disease (Allebeck, 1989). Reasons for the heightened mortality rate due to cardiovascular disease probably include; heavy smoking, poor nutrition, lack of access to health care services, and the side effects of some antipsychotic medications.

In summary, schizophrenia is an extremely debilitating disorder which is typified by a diverse range of symptoms. Outcome for a patient is difficult to predict, and it appears that the course of the illness depends on a number of sociodemographic, premorbid and clinical features.
1.2 Why is the study of cognition important in schizophrenia?

'this is not a disorder of symptoms alone' (Green, 1999, p. 198).

The last ten years have seen a major change in our understanding of schizophrenia. There is now a widespread recognition that neurocognitive deficits are an integral feature of the disorder, and that symptoms alone cannot account for many of the mental and behavioural problems that are exhibited. The evidence for this assertion comes from a variety of sources. Firstly, some cognitive deficits are evident before the onset of psychosis and persist long after symptoms have abated (Nuechterlein et al. 1992; Cornblatt & Erlenmeyer-Kimling, 1985; Asarnow et al. 1977). Secondly, cognitive deficits are also found in some first degree relatives (Green et al. 1997; Keefe et al. 1997; Grove et al. 1991; Mirsky et al. 1992) and in individuals considered to be prone to psychosis (Lenzenweger & Korfine, 1994; Lenzenweger et al. 1991). This suggests that neurocognitive deficits may reflect a predisposition or vulnerability to the disorder. Thirdly, imaging studies have confirmed dysfunctional neural circuitry in schizophrenia which is independent of symptomology (O'Leary et al. 1996; Yurgelun-Todd et al. 1996; Dolan et al. 1995; Weinberger et al. 1986). Fourthly, there is an association between cognitive deficits and functional outcome suggesting that even with symptom remediation, cognitive deficits may still prevent patients from functioning adequately in the social environment (Green, 1996). Indeed this observation is true for any disease which adversely affects cognition (Heaton & Pendleton, 1981).

These findings, therefore, indicate that cognitive deficits are an intrinsic feature of schizophrenia and that an investigation of their cause, at both a cognitive and physiological level, may go some way to help our understanding of this disorder. Another reason why the study of cognition is important in schizophrenia is that this may provide an additional focus for treatment (Green, 1999). An understanding of the specific neuropathology behind the cognitive deficits enables potential treatments to be developed which could remediate the
impairment. Indeed, Friedman et al. (1999a) make a number of suggestions for pharmacological strategies that may reduce the cognitive deficits in schizophrenia. For example, it is suggested that drugs that increase dopamine in the prefrontal cortex, such as atypical antipsychotics, may improve working memory and concentration in schizophrenia, and drugs that increase cortical cholinergic activity, such as AchE inhibitors and M1/M4 muscarinic agonists, may improve memory and language use.

In summary, the investigation of the cognitive deficits in schizophrenia has the potential to provide telling insights into the pathophysiology of the disorder, as well as providing the opportunity for the development of treatments which may help remediate this impairment.

1.3 What are the Cognitive Deficits in Schizophrenia?

i) Executive Function

Executive function refers to a constellation of higher level cognitive abilities which enable an individual to plan and execute goal-directed operations (Velligan & Bow-Thomas, 1999). As a multi-dimensional concept, executive function incorporates a number of cognitive skills including; the ability to co-ordinate and guide lower level cognitive processes such as memory and attention; the planning, initiation and sequencing of behaviour; self monitoring; and the inhibition of behaviour which is inconsistent with a specific goal (Lezak, 1995; Frith, 1992). Independent and productive living are mediated by executive skills and therefore impairment in any executive function is likely to have an adverse effect on an individuals’ social functioning and self care abilities.

One of the most widely investigated aspects of executive function which has been found to be impaired in schizophrenia is that of attention. Indeed, specific deficits in attention have been
reported in schizophrenia since the time of Kraeplin (1921) and Bleuler (1911). Although there is no universally accepted definition of attention (Johnston & Dark, 1986), there is agreement that the concept of attention can be subdivided into a number of dissociable components;

1) Selective attention. This refers to the ability to maintain focus on important stimuli or ideas in the presence of other distracting stimuli (van Zomeren and Brouwer, 1990; Johnston and Dark, 1986).

2) Sustained attention or vigilance. This describes the ability to maintain attention over a period of time (van Zomeren and Brouwer, 1990; Sheer and Schrock, 1986).

3) Divided attention. This is concerned with the ability to attend or respond to more than one task at the same time or to several elements within a task (van Zomeren and Brouwer, 1990; Sohlberg & Mateer, 1989; Stuss et al. 1989).

4) Switching or set shifting attention. This refers to the ability to shift focus or attention from one stimulus to another (Mirsky, 1989; Sohlberg & Mateer, 1989).

Of these component processes, it has been widely reported that patients with schizophrenia have a selective deficit in set shifting attention. This has been observed in a number of experimental paradigms using different attentional measures, including: cross-modal switching studies (Sutton & Zubin, 1965), the Wisconsin Card Sorting Test (Green et al. 1992; Braff et al. 1991) and the Continuous Performance Test (Sax et al. 1998). Although it can be argued that none of these tests are 'pure' measures of set shifting ability but rather involve more than one aspect of attention (Smith et al. 1998), where studies have directly compared different attentional abilities within the same experimental paradigm a selective deficit in set shifting ability has been reported (Smith et al. 1998; Zubin, 1975).

1 Kraeplin (1921) noted that patients with dementia praecox exhibited 'a certain unsteadiness of attention' whilst Bleuler (1911) noticed that 'acute attention was lacking'.

2 For example, the WCST involves the subject attaining a concept, maintaining a concept and then switching from one concept to another.

3 Deficits in selective and sustained attention have been reported in schizophrenia, but these have been explained as being due to the consequences of symptoms and task work load rather than being an enduring characteristic of the illness (e.g., Spring et al. 1989; Nuechterlein et al. 1986).
On a behavioural level, failure to shift attentional set may manifest as perseveration, stemming from a failure to inhibit the response to a previous item that was being attended to (Elliot et al. 1998; 1995). Neuropathologically, such a deficit has been associated with a combined deficit involving both frontal cortical and striatal mechanisms (Elliot et al. 1995).

Another aspect of executive function reported to be impaired in schizophrenia is that of planning ability (e.g., Morice & Delahunty, 1996). Planning involves the simultaneous storing and manipulation of information and experimentally is often investigated using the Tower of Hanoi Test. This test consists of three or four discs placed on pegs on a pegboard. The subject is required to rearrange the discs in order to match a target pattern although there are certain constraints to be borne in mind whilst completing the task. In practice, the task involves the completion of a number of sub goals – moving individual pegs, whilst keeping in mind the main goal – matching the pattern. The complexity of the task can be manipulated by changing the starting position of the pegs relative to the target pattern and in this way the cognitive demands of the task can be increased or decreased. In order to do well in the task the subject has to plan a sequence of moves in the mind prior to the initiation of the movement sequence. Patients with schizophrenia consistently perform poorly on this test (Schmand et al., 1992; Goldberg et al., 1990), and on revised versions of this test such as the Tower of London (Rushe et al. 1999a; Morris et al. 1995; Andreason et al. 1992) and Stockings of Cambridge (Hutton et al., 1998; Pantelis et al., 1997).

Cognitive explanations for schizophrenic patients’ poor performance on this test have suggested a general failure of inhibitory mechanisms because the patient will often begin trying to solve the problem without adequate forethought, consequently resulting in poor performance (Elliott et al. 1998). This suggestion is in accordance with the influential hypothesis of Frith (1987; 1992), that self-monitoring processes are impaired in schizophrenia.
Neuropathological explanations for this deficit have emphasised the similarity between the performance of patients with schizophrenia on this test and the performance of patients with frontal lobe resections (Pantelis et al. 1997; Owen et al., 1990). However, some authors have not found such a clear similarity between the performance of these two patient groups, suggesting a more distributed pathology in schizophrenia, perhaps involving neural connections between the prefrontal cortex and the medial temporal lobe (Rushe et al., 1999a). Indeed, it has been suggested that performance on this type of task requires that the frontal and temporal lobes be in ‘continuous conversation’ (Weinberger, 1991). Furthermore, on the basis of their findings that patients with schizophrenia exhibit an overall cognitive slowness or ‘bradyphrenia’ on the Tower of London task, Pantelis et al. (1997) suggest that subcortical structures or frontal-striatal-thalamic circuits may also be involved in the disorder.

In addition to the deficits involving executive function in schizophrenia, impairments involving memory function have also been identified.

ii) Memory

Human memory is considered to comprise a number of dissociable domains (see Figure 1.1 overleaf), with an elementary distinction being made between memory for events in the short term and memory for events in the longer term. Short Term Memory (STM) or primary memory acts as a brief storage facility for information, and can hold a limited number of items for a duration of up to 30 seconds at a time. In contrast, Long Term Memory (LTM) or secondary memory holds all information that needs to be retained for much longer periods of time and is considered to have unlimited capacity. The interaction between STM and LTM was elucidated in recent years with the development of the working memory model (Baddeley, 1986) which describes the process by which information is retrieved from long term memory and held in mind for the purpose of guiding behaviour without the aid of
referential stimuli in the outside world. Prior to the development of the working memory model, STM was considered to play little role in active information processing.

**Figure 1.1 Divisions within the human memory system**

![Diagram of memory system]

Further dissociations have been made between stores of information within LTM with a distinction being made between procedural and declarative memory. Procedural memory holds knowledge of 'how to do' things and is concerned with motor skills and behaviours which cannot be inspected consciously. For example, riding a bike is a complex motor skill which is difficult to describe, and most language speakers can not describe the complex grammatical rules they use whilst speaking. Declarative memory, in contrast, holds items of information which can be inspected consciously and can be further subdivided into semantic memory and episodic memory. Semantic memory is a store of factual knowledge about the world and has been described as a mental thesaurus (Tulving, 1972). This store would contain information such as 'Paris is the capital of France' or 'spiders have eight legs', and in everyday terms could be described as the 'knowledge' that an individual possesses. Episodic memory, on the other hand, is responsible for storing a record of our past experiences, the places we have been, the people we have met and the objects we have encountered. This aspect of memory can be considered autobiographical memory because of the subjective
nature of the information contained within. Recalling what we had for breakfast, or what we did on holiday, both utilise information held in episodic memory.

In schizophrenia, general memory deficits have been well documented (Aleman et al. 1999; Goldberg et al. 1993; Saykin et al. 1991; McKenna et al. 1990), and have been found to be disproportionate to the general level of intellectual impairment and to other aspects of cognitive function (Saykin et al. 1991; McKenna et al. 1990). Patient factors such as psychotic distraction, lack of co-operation or poor motivation cannot adequately explain these deficits (Clare et al. 1993), and neither can the actions of anticholinergic medications because acute administration of these drugs has minimal impact on cognitive function (King, 1990) and long term exposure to anticholinergics is not related to general intellectual impairment (Owens and Johnstone, 1980). Furthermore, a meta analysis performed by Aleman (1999) found that neither age, nor medication status, duration or severity of illness or positive symptomology were associated with the memory deficit in schizophrenia. However, negative symptoms were found to be significantly associated with the deficit. Within the subdivisions of memory it seems that some domains are impaired whilst others are intact.

Semantic memory in schizophrenia

Indications that semantic memory is disproportionately impaired in schizophrenia were first reported by Tamlyn et al. (1992), who administered a wide battery of memory tests to a group of schizophrenic patients and found a marked deficit in the patients’ abilities to differentiate between true “rats have teeth” and nonsense “desks wear clothes” sentences. These results were considered to reflect deficient semantic processing. Further studies have since confirmed this finding using a variety of different measures of semantic memory (Laws et al. 2000; Granholm et al. 1998; McKay et al. 1996; Joyce et al. 1996; Chen et al. 1994; Clare et al. 1993; Allen et al. 1993). Recent attention has focussed on whether this deficit reflects a degradation of items within the semantic store (a storage problem) or if the deficit reflects
problems in accessing intact items within the semantic store (an access problem). According to Warrington & Shallice, (1979), storage and access disorders can be clearly distinguished experimentally;

Firstly, storage disorders reflect a permanent loss of the item from the lexicon, so, for example, a person may never recall the name of President Bush no matter what prompts or clues are given. An access disorder, on the other hand may be distinguishable by fluctuations in naming ability, so that sometimes a person may remember the name of President Bush, whereas on another occasion they may not. Secondly, storage disorders are resistant to the influence of priming or cueing during naming, whereas naming can be facilitated by priming or cueing in an access disorder. Thirdly, in storage disorders less frequent items tend to be lost from the lexicon first, resulting in a discrepancy between naming ability for frequent and infrequent items. In access disorders, both frequent and infrequent items may be equally difficult to name. Fourthly, in storage disorders superordinate information, such as 'is the president', is better preserved than subordinate information, such as 'his father was president too'. In access disorders superordinate information and subordinate information may be equally affected.

Using these distinctions several authors have attempted to investigate whether the semantic memory deficit in schizophrenia reflects a storage or an access problem. Allen et al. (1993) found inconsistency in the naming ability of schizophrenic patients in a verbal fluency task suggesting an access disorder. Joyce et al. (1996) found that naming ability could be improved with cueing, again suggesting an access, rather than storage, disorder.

However, Laws et al. (2000) investigated the access - store dichotomy in a group of chronically hospitalised schizophrenics using two of the criteria of Warrington & Shallice (1979), consistency and word frequency. They found that storage problems were far more prevalent than access disorders in this patient group suggesting that severity of illness may determine the precise nature of the semantic memory deficit, with chronically ill patients
displaying a storage disorder whilst access disorders are more likely to be displayed by patients who are not as acutely ill.

Episodic memory in schizophrenia

Episodic memory is involved in all tasks that require a conscious recollection of information or events that were previously experienced. Experimentally, a number of different methods have been used to investigate episodic memory in schizophrenia, including story recall, design recall, design learning and word list learning. In addition, several batteries of memory tests have been used to investigate episodic memory in this patient population, including the Rivermead Behavioural Memory Test (Wilson et al. 1985) and the California verbal learning test (Delis et al. 1987). The results of such studies have overwhelmingly indicated that patients with schizophrenia have an impairment in episodic memory compared to controls (Mellers et al. 2000; Cannon et al. 2000; Danion et al. 1999; Rushe et al. 1999b; Oie et al. 1999; Putnam & Harvey, 1999; Paulson et al. 1995; Huron et al. 1995; Beatty et al. 1993; Goldberg et al. 1993; Tamlyn et al. 1992). In addition, this deficit was found to be present early on in the course of the illness (Seidman et al. 1998), and one study reported that episodic memory tests are able to distinguish between subgroups of patients with schizophrenia, with treatment resistant patients performing significantly poorer than treatment responsive patients even when factors such as I.Q., years of education and exposure to anticholinergics are taken into account (Lawrie et al. 1995). On the basis of these findings the authors suggest that an episodic memory deficit may be used as a marker for poorer outcome, as a patient with such a deficit may find independent living and treatment compliance difficult to maintain.

In terms of the neuropathological basis for such an impairment, anterior hippocampal volumetric reductions on MRI scans as well as irregularities in the medial and left temporal region have been implicated (Bogerts et al. 1985; Brown et al., 1986; Jakob & Beckman,
A PET investigation has also revealed hippocampal dysfunction during an episodic memory task in a group of schizophrenic patients (Heckers et al. 1998).

Procedural memory in schizophrenia

Procedural memory is concerned with memory for motor skills and well learned habits and has rarely been studied in relation to schizophrenia. Goldberg et al. (1993) gave a group of schizophrenic patients and controls a motor task to perform where the subject is requested to keep a stylus in contact with a target area on a rotating disc (a pursuit rotor task). Performance on this task did not differ between patients and controls. However, Clare et al. (1993) administered three different types of procedural memory tasks to a group of schizophrenic patients – a pursuit rotor task, a jigsaw completion task and a task where the subject had to learn a linguistic / perceptual skill. Overall the schizophrenic patients performed at a lower level than controls, although their rate of acquisition and retention of each skill was equivalent to that of the controls. This was considered to indicate that different mechanisms may be responsible for learning and performance respectively, and that it is only the performance mechanism that is impaired in schizophrenia. Schroder et al. (1996) used the Tower of Toronto test to investigate procedural memory in schizophrenia. In this test the subject is required to change the position of coloured pegs on a peg board in order to match a target configuration, although there are several movement constraints which must be borne in mind whilst completing the task, e.g., only one disc may be moved at a time. Patients’ performance was found to be impaired on this task. Schmand et al. (1992) and Gras-Vincendon et al. (1994) similarly found that schizophrenics’ performance on the Tower of Toronto Test was impaired although it did improve on repetition of the test. The degree of this improvement did not differ between schizophrenic patients and healthy controls, although patients continued to score significantly lower than controls on repetition of the test. In line with the findings from Clare et al. (1993), this again suggests that different mechanisms may be responsible for learning and performance respectively. Reports of associations between
negative symptoms and procedural memory, as measured by Tower of Toronto type tests, suggest the involvement of the medial frontal cortex in the performance of this task (Schroder et al. 1996; Andreason et al. 1992). However, it is a matter of debate whether tests like the Tower of Toronto are measures of procedural memory or whether they are more a measure of subject’s planning ability.

Recognition versus recall in schizophrenia

The successful retrieval of information from memory can be indicated in a number of ways, but experimentally the distinction is often made between the recognition that something has been encountered before, and the explicit recall of previously presented material. For example, in a recognition paradigm a subject must simply state whether an item of information has been previously encountered, such as a face or a word, whereas in a recall paradigm the specific recounting of previously presented material is expected, such as the recall of a story. In schizophrenia, most studies of recognition memory have focussed on verbal recognition where deficits have often (e.g., Crespo-Facorro et al. 2001; Tracey et al. 2001; Gruzelier et al. 1999; Rushe et al. 1999b; Kayser et al. 1999), but not always, (e.g., Oie et al. 1999; Rushe et al. 1999b; Nathaniel-James et al. 1996; Goldberg et al. 1993; Beatty et al. 1993; Vinogradov et al. 1997; Johnson et al. 1977), been reported.

The situation with regard to non verbal recognition in schizophrenia is even less clear, with few studies being carried out, and the studies that have been done have tended to focus on one type of non verbal material whilst ignoring others (e.g., Conklin et al. 2000; Gruzelier et al. 1999; Nathaniel-James et al. 1996; Goldberg et al. 1993; Clare et al. 1993; Tracy et al. 2001). In addition, some studies have used test stimuli which are easy to verbalise and therefore are not pure measures of visual memory (Tracey et al. 2001; Putnam & Harvey, 1999). This is a significant problem because it undermines attempts to identify a specific functional impairment, and it also undermines attempts to identify the anatomical basis of such an
impairment because visual memory and verbal memory are considered to be mediated by the right cerebral hemisphere and left cerebral hemisphere respectively.

Of the studies of non verbal recognition that have been carried out in schizophrenia, most have used faces as their experimental stimuli (Gruzelier et al. 1999; Nathaniel-James et al. 1996; Goldberg et al. 1993; Clare et al. 1993), although findings are inconclusive with some studies reporting an impairment (Clare et al., 1993; Gruzelier et al. 1999) whilst others do not (Nathaniel-James et al. 1996; Goldberg et al. 1993). Other investigations have used non verbal material such as geometric figures (Tracy et al. 2001; Putnam & Harvey et al. 1999; Oie et al. 1999; Elliot et al. 1995; 1998; Hutton et al. 1998), nonsense figures (Oie et al. 1999) and reproductions of histological specimens (Cutting, 1979). In addition, recognition memory for the location of geometric figures on a display has also recently been investigated in schizophrenia (Elliot et al. 1995; 1998; Hutton et al. 1998).

All of these studies have reported an impairment in schizophrenia, although assumptions as to a general deficit in non verbal recognition can not be reliably made as too few studies have been conducted, and few patients have been tested using more than one measure of non verbal recognition. In addition, many of the studies used small patient numbers who were not representative of the general population of adult patients with schizophrenia. For example, Oie et al. (1999) explored non-verbal recognition memory in a group of 19 adolescents with schizophrenia, and Elliott et al. (1998) tested a group of 12 schizophrenic patients with preserved intellectual function (I.Q. >90). The findings of impaired recognition memory in these studies should probably not be extrapolated to the adult schizophrenic population.

In terms of recall memory in schizophrenia, most studies have reported a clear deficit (Putnam & Harvey, 1999; Paulsen et al. 1995; Tamlyn et al. 1992; Clare et al. 1993), which is evident even in the presence of intact recognition memory (Rushe et al. 1999b; Oie et al. 1999).
1999; Beatty et al. 1993; Goldberg et al. 1993). Indeed, the meta-analysis conducted by Aleman et al. (1999) did indicate that recall memory was significantly affected in schizophrenia, although not all studies have reported a recall deficit (Nathaniel-James et al. 1996).

Explanations of an impairment in recall with preservation of recognition have emphasised the similarity between this pattern of impairment and that of patients with organic amnesia (e.g., Rushe et al. 1999b), and candidate brain regions have been suggested to include prefrontal neural systems (Goldberg et al. 1993; Beatty et al. 1993), and subcortical areas (Beatty et al. 1993). On a cognitive level, impaired recall with intact recognition is often considered to reflect a retrieval deficit and less efficient consolidation of material in memory (Aleman et al. 1999). It could be suggested that differences in performance between the two types of task merely reflect task difficulty, with recall tests being much harder to perform than recognition tests. However, studies which have controlled for task difficulty have still found greater impairment in recall than in recognition (Calev, 1984a; 1984b).

Short Term Memory (STM) in schizophrenia

STM can be split into at least two distinct subsystems, one involved in the short-term retention of verbal information, the other involved in the short-term retention of visuo-spatial information (Baddeley, 1986, 1992). In schizophrenia, studies of STM have tended to focus on verbal retention and have used the digit span task for this purpose. Results from these studies have been inconclusive with some authors reporting no deficit in short term verbal memory (Goldberg et al. 1993; Park & Holzman, 1992; Tamlyn et al. 1992; Kolb & Whishaw, 1983), whilst others report an impairment (Aleman et al. 1999; Conklin et al. 2000; Goldberg, 1998; Weiss et al, 1988). Where found, these deficits have sometimes been explained as being due to attentional dysfunction, with patients being unable to appropriately allocate processing resources to the digit span test (Kreimen et al. 1992; Weiss et al. 1988).
However, these conclusions have been challenged as Goldberg et al (1998) found that actual limitations in STM capacity, and not attentional dysfunction, were to blame for patients’ poor performance. Of the few studies that have investigated spatial short-term memory in schizophrenia, most have reported a deficit compared to healthy volunteers (Elliot et al. 1998; Hutton et al. 1998; Pantelis et al. 1997). Impaired short-term memory for both verbal material and visuo-spatial material suggests that this impairment is not restricted to one subsystem within STM. However, this suggestion can only be confirmed with studies which directly compare performance on tests of verbal STM and visuo-spatial STM in a schizophrenic sample. To the author’s knowledge no studies have explored this issue to date.

Working memory in schizophrenia

Working memory can be considered an extension of the simplistic STM model because it incorporates the core feature of STM, holding information ‘on line’, but also incorporates additional features which explain how the information which is held on line can be manipulated and utilised to guide behaviour. According to Baddeley (1981, 1986), working memory is comprised of a central executive, an articulatory loop, a visuospatial scratchpad and a primary acoustic store. The central executive is at the top of the hierarchy and can be considered the crucial feature of the working memory model because it is involved in any task in any sensory modality which makes cognitive demands. Its purpose is to allocate attentional resources to incoming information and to direct the operations of the other components, the ‘slave systems’, (Baddeley, 1990). The function of the central executive has been compared to that of the model of attention suggested by Norman & Shallice (1980). Here, a supervisory system is proposed which has limited processing capacity but is used for specific information processing tasks; 1) conscious thought and deliberation, 2) planning, 3) difficult tasks, 4) new or novel situations, 5) in circumstances where learned automatic responses must be inhibited.

Subsidiary to the central executive are the modality specific slave systems. The articulatory loop deals with verbal material that is being rehearsed (e.g., remembering a telephone
number) but is also used as a temporary store to hold words we are preparing to speak. The visuospatial scratchpad performs similar operations to the articulatory loop but is specific to visual information (size, shape, colour) and spatial information (mental picture of a familiar route). The primary acoustic store is concerned with non-verbal auditory information such as pitch and loudness, and has been likened to an ‘inner ear’.

Empirical investigations of working memory in schizophrenia have overwhelmingly indicated a deficit in the spatial working memory slave system (Minor & Park, 1999; Fleming et al., 1997; Spindler et al., 1997; Keefe et al., 1995). This deficit has been shown to be independent of the patients’ general cognitive state and is not associated with their symptom display (Snitz et al., 1999; Park et al., 1999; Park & Holzman, 1993; 1992). Furthermore, studies of spatial working memory in conjunction with studies of spatial span have indicated that poor performance on spatial working memory tasks is associated both with decreased capacity for holding information on line, and an inefficiency in manipulating this information during cognitive operations (Elliot et al. 1998, Hutton et al., 1998, Pantelis et al. 1997). In contrast to the clear impairment shown in spatial working memory, there is conflicting evidence for verbal working memory deficits in schizophrenia with some authors reporting a deficit (Conklin et al. 2000, Granholm et al. 1997) whilst other authors report no impairment (Park & Holzman, 1992).

The conflicting findings between schizophrenics’ performance on spatial working memory tasks compared to verbal working memory tasks suggests firstly, that the impairment is restricted to slave systems leaving the central executive unaffected, and secondly, that the slave systems are relatively independent of each other. Indeed, the suggestion that the central executive is unimpaired in schizophrenia and that slave systems operate independently of

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4 The primary acoustic store was not part of Baddeley’s original model but was added by Salame & Baddeley in 1982. However, this part of working memory has not been studied in relation to schizophrenia and so will not be considered further.
each other has some empirical support (Spindler et al. 1997). However, other studies have yielded conflicting results. Granholm et al. (1997) found that task difficulty influences verbal working memory performance, and Snitz et al. (1999) found that patients completing a visual working memory task were vulnerable to distraction. Both of these findings suggest reduced availability of central executive resources in schizophrenia. Furthermore, given the similarity between the central executive and the supervisory attention system, any suggestion that the central executive is unimpaired in schizophrenia must be reconciled with the wealth of data indicating that attention is impaired in schizophrenia (e.g., Braff, 1993).

However, it has been suggested that working memory is an important component of many cognitive tasks and not just those that simply involve the manipulation of visuo-spatial or verbal material held in mind. In particular, any task that requires reasoning or problem solving skills incorporates a working memory component because typically such tasks require the continual updating and manipulation of mental concepts as well as the shifting of plans (Stone et al, 1998; Goldman-Rakic & Selemon, 1997). Indeed, tests which measure these abilities, e.g., The Tower of London Test (Shallice, 1982), the Stroop Test (Stroop, 1935), and the Wisconsin Card Sorting Test (Milner, 1963) are usually performed poorly by patients with schizophrenia suggesting that working memory is an important component of these tasks (e.g., Schooler et al. 1997; Andreason et al, 1992; Franke et al, 1992).

Despite some of the unresolved questions relating to the status of working memory subsystems in schizophrenia, there is a substantial body of opinion which proposes that a working memory deficit may be at the core of many of the cognitive deficits apparent in the disorder (for a review see Goldman-Rakic, 1994). Indeed, such a suggestion may be intuitively appealing because without an intact working memory system, a person would be unable to efficiently retrieve and utilise information from past experience for the purpose of

5 These authors also found an impairment in verbal working memory in the nonpsychotic relatives of schizophrenic patients prompting a suggestion that the backward digit span task could be used as a valuable indicator of genetic susceptibility.
self-directed behaviour, and such a deficit has been proposed to underlie not only the
cognitive impairment in schizophrenia, but also the behavioural disorganisation, negative
symptoms, and some positive symptoms that are also displayed in the disorder (Goldman-
Rakic & Selemon, 1997). Furthermore, Goldman-Rakic and Selemon (1997) suggest that a
failure of the long term memory retrieval mechanism in working memory may account for
impoverished thought processes in schizophrenia, and that problems holding information on
line, or problems erasing information after it has been held for several seconds, may account
for the repetitive or perseverative thought processes which are also a feature of the illness.

Further support for the working memory hypothesis in schizophrenia has come from
neurophysiological studies which have suggested that firstly, the prefrontal cortex is
important for working memory operations (Moskovitch, 1994a, 1994b; Moskovitch &
Winocur, 1992; Owen et al. 1990; Janowsky et al. 1989; Jetter et al, 1986; Petrides & Milner,
1982), and secondly, that this brain region may be implicated in the general pathophysiology
of the disorder (Ananth et al. 2002; Gur, 2000; Crespo-Facorro 1999; Buchanan, 1998;

1.4 Neurotransmitter systems and cognition in schizophrenia

Despite the evidence from neuropsychological and neuroimaging studies which suggests that
one of the key features of schizophrenia is an impairment in the prefrontal cortex, the precise
pathophysiology in this region is still unclear. However, there is mounting evidence that
neurotransmitter systems play a role in the cognitive dysfunction associated with this region,
particularly dopamine and serotonin.
i) Dopamine and serotonin

Findings of reduced D1 receptors in the prefrontal cortex of patients with schizophrenia suggest that this receptor may play an important role in the cognitive deficits observed in the disorder (Abi-Dargham et al. 2002; Okubo et al., 1997). Indeed, evidence from animal studies support this suggestion as dopaminergic antagonists, especially those that are selective for the D1 receptor, impair performance in a delayed response task (Didrikson, 1995). Furthermore, the injection of selective D1 receptor antagonists (e.g., SCH39166 or SCH23390) and non selective D1 antagonists (e.g., haloperidol) to the prefrontal cortex of monkeys induces a dose dependent impairment in performance in the delayed response task. This impairment is not triggered after injection of selective or non selective D2 antagonists (sulpiride or raclopride) (Sawaguchi and Goldman-Rakic, 1994). In humans, a correlation has been found between the number of D1 receptors in the prefrontal cortex and performance on the WCST and the BPRS negative symptom scores (Okubo et al. 1997). This suggests that reduced numbers of D1 receptors in the prefrontal cortex and the resulting decrease in dopaminergic turnover are the basis for at least some aspects of cognitive dysfunction in schizophrenia (Friedman et al. 1999a).

More generally, a wealth of studies have shown that dopamine manipulation has an influence on cognitive function, particularly working memory, and similar effects are observed whether the subjects are animals, healthy controls or patients (Mehta et al. 2001; Granon et al. 2000; Mehta et al. 1999; Muller et al. 1998; Luciana et al. 1998; Kimberg et al. 1997; Zahrt et al. 1997; Murphy et al. 1996; Arnsten et al. 1995; Sahakian et al. 1985; Brozowski et al. 1979; Goldman et al. 1971).

However, over the years an inconsistent picture has emerged with some studies reporting that dopamine depletion impairs working memory (Brozowski et al. 1979; Goldman et al. 1971) whilst other studies have found that working memory is impaired when dopamine levels are
elevated (Zahrt et al. 1997; Murphy et al. 1996; Sahakian et al. 1985). There have been two attempts to explain these conflicting findings. Robbins (2000, 1985) suggests that there is a u shaped relationship between working memory and dopamine levels in the prefrontal cortex with both extreme high and extreme low levels impairing performance. Alternatively, Granon et al. (2000) suggests that the baseline levels of performance have an influence on subsequent response to dopamine manipulation. Subjects achieving a low score on cognitive tests at baseline will show an improvement in performance with dopamine depletion, whilst high scorers will show a decrement in performance. This latter suggestion has some empirical support (Granon et al. 2000; Kimberg et al. 1997).

In summary, there is considerable evidence that the cognitive functions mediated by the prefrontal cortex are dependent on the activity of dopamine in this region, and that either a lack of dopamine, or an excess, can impair cognitive processes. In schizophrenia it has been widely recognised that it is a deficiency in prefrontal dopamine, rather than an excess, that is the cause of the cognitive impairment (Ichikawa & Meltzer, 1999; Honey et al., 1999; Lieberman et al. 1998; Davis et al. 1991; Sawaguchi & Goldman-Rakic, 1991). Other evidence for an impairment in prefrontal dopamine in schizophrenia includes; studies which have found that schizophrenic patients have disturbed levels of mRNA expression for some classes of dopamine receptors in the prefrontal cortex (Meador-Woodruff et al, 1997; Stefanis et al. 1998), and a study which reported reductions in proteins which play a critical role in dopamine neurotransmission in the prefrontal cortex of patients with schizophrenia (Akil et al. 1999).

However, this assertion leads to an apparent paradox because the class of medication that has shown some success in remediating cognitive function in schizophrenia, the atypical antipsychotics, are dopamine antagonists. On the basis of the assumption that dopamine activity in the prefrontal cortex is essential for cognitive function, then an antagonism of dopamine would be expected to further exacerbate the existing cognitive impairment. Indeed,
Cohen & Servan-Schreiber (1994) 'find it difficult to reconcile the fact that neuroleptics block dopamine activity but at the same time improving (or at least not further impairing) schizophrenics' poor performance, if, as we have hypothesised, performance deficits are due to a reduction of dopamine in the first place' (p 417).

In the light of this paradox, it seems that explanations for the neurochemical remediation of the cognitive impairment in schizophrenia might preferentially lie outside of dopamine activity in the prefrontal cortex, perhaps involving neurotransmitter activity elsewhere which may elicit an effect on prefrontal dopamine. Indeed, this suggestion has been made by several authors (Friedman et al. 1999a; Ichikawa & Meltzer, 1999; Sharma & Mockler, 1998; Sanyal & Van Tol, 1997).

Friedman et al. (1999a) detail the influence that antagonism of serotonergic receptors outside the cortex has on prefrontal dopamine. They note that firstly, all atypical antipsychotics except amisulpride antagonise 5-HT2A receptors. This results in the activation of dopaminergic neurones located in the ventral tegmental area which extend to the substantia nigra, the nucleus accumbens and the prefrontal cortex. Subsequently, this leads to an increase in prefrontal dopamine turnover and a consequent improvement of the cognitive functions that are mediated by the prefrontal cortex. Evidence to support this suggestion has been provided in studies where the administration of drugs which selectively antagonise 5-HT2A receptors such as ritanserin or MDL 100,907, or which possess 5-HT2A blocking properties, such as risperidone or clozapine, do increase prefrontal dopamine turnover (Friedman et al. 1999a; Hertel et al. 1996; Schmidt & Fadayel, 1995). Similarly, direct injection of the 5-HT2A antagonist ritanserin into the prefrontal cortex also increases dopamine release in this region (Pehek, 1996). Other authors have similarly noted that antagonism of 5-HT2A receptors does result in an enhancement of dopamine activity in the prefrontal cortex (Leyson et al. 1998; Lieberman et al. 1998; Meltzer, 1999; Kuroki et al. 1999). Svensson et al. (1995) further proposed that the remediation of negative symptoms by atypical antipsychotics is due to
antagonism of 5-HT2A receptors which results in increased burst firing of dopaminergic neurones in the medial prefrontal cortex. Furthermore, there has been evidence from PET studies using normal subjects that serotonin modulates dopamine function (Smith et al. 1997).

Some evidence, therefore, suggests that antagonism of 5HT2A receptors restores dopaminergic neurone activity in the prefrontal cortex and through this action has a positive effect on cognitive function in schizophrenia. More generally, there is unquestionable evidence that serotonin plays an important role in cognitive function and this influence may not be restricted solely to 5HT-2A receptors (for a review see Buhot et al. 2000 or Meneses et al. 1999).

However, in addition to suggestions about the role that dopamine and serotonin play in the cognitive deficits in schizophrenia, a recent hypothesis which attempts to explain the therapeutic effect of atypical antipsychotics also needs to be considered in terms of cognition.

ii) The Fast Dissociation Hypothesis

This is a new hypothesis which attempts to explain the neurochemical basis of the clinical therapeutic superiority of atypical antipsychotics over typical antipsychotics in schizophrenia. It centres on the D2 dopamine receptor and the affinity and dissociation speed of antipsychotic medication. There is now very strong evidence that antipsychotic action is dependent on the blockade of dopamine D2 receptors. Indeed, as Kapur and Seeman (2001) point out, attempts to produce an antipsychotic effect without D2 blockade have been unsuccessful. For example, drugs which act only on 5-HT2 receptors (MDL-100907: Report S, 1999), D4 receptors (L-745,850: Bristow et al, 1997), or D1 receptors (SCH-23390: Gessa et al. 1991) have not shown any antipsychotic properties. Neither have compounds which act on both 5-HT2 and D4 receptors (fanansarin: Truffinet et al. 1999). Therefore, it can be
reliably assumed that the therapeutic effect of antipsychotic medication is due to the blockade of dopamine D2 receptors.

However, what is unclear is how the typical and atypical antipsychotics differ in terms of their therapeutic profile if the mechanism of action of both of them is simply the blockade of dopamine D2 receptors. Kapur & Remington (2001) suggest that the essential difference between typical and atypical antipsychotics is that the atypical antipsychotics have a lower affinity for D2 receptors than typical antipsychotics. However, because affinity values are defined by the rate at which the drug moves on and off the receptor, and because the difference between typical and atypical antipsychotics is owing to detach latency rather than attach latency (Kapur & Seeman 2001), it is more precise to define the difference between atypicals and typicals in terms of their dissociation rates from the dopamine D2 receptor. As an example of this, Sailer and Salama (1993) reported that 40 mg of clozapine produced 61% D2 occupancy within 30 minutes, which reduced to 0% 4 hours later. Conversely, 1 mg of haloperidol produced 57% occupancy at 30 minutes, which increased to 62% four hours later.

In terms of the therapeutic consequences of this fast dissociation, the faster the dopamine D2 dissociation, the more rapidly the drug responds to surges in endogenous dopamine. This is because drugs which drop off the receptor easily allow endogenous dopamine access to the receptor. In addition, several studies have found that when there is sustained D2 occupancy, as is found in slow dopamine D2 dissociating conventional antipsychotics, symptoms similar to tardive dyskinesia can develop. This is because sustained blockade leads to tolerance and up regulation. In contrast, administration of antipsychotic treatment which does not lead to sustained D2 occupancy (e.g., intermittent administration of haloperidol), as is found in fast dopamine D2 dissociating antipsychotics, does not lead to such symptoms (See & Ellison, 1990). Here transient occupancy avoids tolerance and up regulation and makes the system more sensitive to the antidopaminergic effects of antipsychotics.
No previous research has explored the association between D2 dissociation speed and the cognitive effects of atypical antipsychotics.

However, despite the attraction of general explanations of the how atypical antipsychotics might exert their beneficial cognitive effects, it is also plausible that each individual antipsychotic exerts an individual and distinguishable effect on cognition. Indeed, there are clear differences between the neurochemical effects of all the atypical antipsychotics. In the following section a description of the neurochemical properties of the atypical antipsychotics will be presented together with a summary of their clinical and cognitive effects.

1.5 Antipsychotic medication and cognitive function in schizophrenia

The ability of typical antipsychotics to remediate some of the symptoms of schizophrenia was serendipitously discovered in the 1950’s when a medication which was thought to be an antihistamine 6 (chlorpromazine) was found to have an effective antipsychotic effect on patients with schizophrenia. Subsequently, chlorpromazine and other conventional antipsychotics were found to produce their antipsychotic effect by blocking dopamine receptors, particularly at the D2 receptor site (Stahl, 1996). However, although these antipsychotics were effective in relieving positive psychotic symptoms due to their affinity for mesolimbic dopamine receptors, they had little effect on the negative symptoms of schizophrenia. In addition, they also had a tendency to produce side effects, such as extrapyramidal reactions and tardive dyskinesia, due to their neurochemical action on the nigrostriatal dopamine pathway.

Concerns about the side effect profile of typical antipsychotics led to the search for drugs which had a more selective affinity for mesolimbic dopamine receptors and less affinity for nigrostriatal dopamine receptors, and which therefore could combine good antipsychotic
potency with low side effect profile. The first of these compounds to be developed was clozapine, which was synthesised in Basle by Sandoz Pharmaceuticals in 1968. A bicyclic compound, it was predicted to be an antidepressant but surprisingly it was found effective in animal models of psychosis, but not in animal models of Parkinsonism. Since then several more of these novel compounds have been developed. These new medications were termed atypical antipsychotics because of their unique pharmacological action, and there are currently five major atypical antipsychotic medications in clinical use in the U.K.

i) Clozapine

Clozapine produces a marked blockade at serotonergic (5-HT\textsubscript{2a}), histaminergic (H1) and adrenergic (\(\alpha_1, \alpha_2\)) receptors but has a considerably lower affinity for dopaminergic (D1, D2) and muscarinic cholinergic receptors (Tandon et al, 1999). The dosage guidelines suggest that between 300-600 mg daily should be optimal for most patients (British National Formulary: BNF). Comparisons of the efficacy of clozapine with typical antipsychotics have shown it was at least as effective in relieving positive psychotic symptoms, but also that it was superior in reducing negative symptoms and side effects in patients with schizophrenia (Kane et al., 1988; Naber et al. 1989). Indeed, several studies have reported success with clozapine in patients thought to be treatment resistant (Avnon & Rabinowitz, 1995; Meltzer et al. 1989; Leppig et al. 1989; Kane et al. 1988). In comparison to other atypical antipsychotics, clozapine has been found to be equally effective in relieving positive and negative symptoms (Tuunainen et al. 2002).

In terms of cognitive function, studies have reported improvements in perceptual speed, attention, and reaction time in patients on clozapine (e.g., Bilder et al. 2002; Hoff et al. 1996; Fujii et al. 1997; Grace et al. 1996), although some studies reported no improvement (e.g., Bender et al. 2001; Daniel et al. 1996; Lindenmayer et al. 1998). Studies of executive

\[6\] antihistamines are a class of medication usually used to treat nasal allergies.
function have reported mixed results, with almost as many studies reporting no improvement or worsening of scores (Lindenmeyer et al. 1998; Buchanan et al. 1994; Hoff et al. 1996; Goldberg et al. 1993), as have reported an improvement (Meyer-Lindenberg et al., 1997; Fujii et al. 1997; Grace et al. 1996). Even when improvements have been observed, these have been very slight in some studies (Mortimer et al. 2003). Meltzer and McGurk (1999) suggest that on the basis of the evidence clozapine may improve some aspects of executive function but not others. Studies of working memory and clozapine treatment have similarly met with mixed results (Galletly et al. 1997; Hagger et al. 1993), as have studies of verbal and visual learning and memory (Hoff et al. 1996; Goldberg et al. 1993; Grace et al. 1996; Buchanan et al. 1994; Daniel et al. 1994; Lindenmayer et al. 1998). However, studies of verbal fluency have, in the main, shown significant improvements following clozapine treatment (Hagger et al. 1993; Buchanen et al. 1994; Galletly et al. 1997). After reviewing all the studies relating to clozapine and cognitive function, Meltzer and McGurk (1999) suggest that the evidence indicates that clozapine has a robust effect in only two cognitive domains – verbal fluency and attention, although there was some evidence that it can improve some types of executive function and verbal learning and memory. However, bearing in mind the considerable methodological differences between each of the studies mentioned, in terms of patient populations and the type of neuropsychological tests used, clear conclusions as to the precise cognitive effects of clozapine are difficult to draw.

ii) Risperidone

Risperidone is a benzisoxazole derivative which has a high binding affinity for both 5-HT2a and D2 receptors, but a lower affinity at α1, α2 and H1 receptor sites (Janssen et al. 1988). It has a markedly different pharmacological profile from both conventional antipsychotics and clozapine (Tandon et al. 1999). Dosage guidelines for risperidone suggest between 4 – 6 mg daily to be optimal (BNF). There is some evidence that risperidone is superior to conventional antipsychotics in terms of its influence on positive symptoms, and in
addition the influence that it has on negative symptoms appears to be dose dependent. However, at low doses risperidone has a milder side effect profile to conventional antipsychotics (Waddington, 2000). It is also equally efficacious in relieving symptoms as olanzapine, clozapine and quetiapine (Tuunainen et al. 2002).

Studies of cognitive improvements on risperidone have revealed a consistent effect on working memory in a variety of experimental paradigms; computerised spatial working memory test (McGurk et al. 1996), digit span distractibility (Green et al. 1997), WAIS-R digit Span backward (Rossi et al. 1997) and verbal working memory (Honey et al. 1999). Interestingly, Honey et al (1999) found that risperidone increased functional activation in prefrontal regions during the execution of a working memory task, suggesting a possible mechanism of action for the improvement. In terms of other aspects of cognitive function, improvements have been found for; attention (Rybakowski & Borkowska, 2002; Stip & Lussier, 1996), executive function (Rybakowsjki & Borkowska, 2002; Chua et al. 2001; Rossi et al. 1996) and multiple aspects of memory (Leander & Wolff, 2002; Bilder et al, 2002; Kern et al. 1999; Daniel et al. 1994). However, even after improvement these scores were often still outside the normal range, and not all studies have shown global positive effects (Hong et al. 2002; Kern et al., 1998; Lindenmeyer et al. 1998; for a review see Meltzer & McGurk, 1999).

iii) Olanzapine

Olanzapine is one of the class of thienobenzodiazepine antipsychotic agents which is similar in structure to clozapine. It has a high affinity for serotonergic (5-HT²a) and muscarinic (M) receptors but a considerably lower affinity for dopaminergic (D₁, D₂), adrenergic (α₁) and histaminergic (H₁) receptors. It also has a minimal α₂ antagonism (Bymaster et al, 1996). The usual dosage range for olanzapine is between 5-20 mg daily (BNF). Controlled trials have demonstrated that olanzapine is superior to traditional antipsychotics in terms of efficacy, especially for negative symptoms, and has a much milder side effect profile (Tollefson &
Kuntz, 1999). It is also equally as effective as clozapine, risperidone and quetiapine at symptom relief (Tuunainen et al. 2002).

Improvements in cognitive function have been reported for patients on olanzapine in terms of memory (Leander & Wolff, 2002; Cuesta et al. 2001; Meltzer and McGurk 1999), attention (Rybakowski & Borkowska, 2002; Bilder et al. 2002; Cuesta et al. 2001; Bender et al. 2001), executive function (Bilder et al. 2002; Bender et al. 2001; Meltzer and McGurk, 1999) psychomotor speed (Bilder et al. 2002; Rybakowski & Borkowska, 2002; Bender et al. 2001; Meltzer and McGurk, 1999; Nowakowska et al. 1999) and perceptual organisation (Bilder et al. 2002; Cuesta et al. 2001).

iv) Quetiapine

Quetiapine has a high affinity for 5-HT2a, α1 and H1 receptors, a lower affinity for the D2 and α2 receptors, and a markedly low affinity for the D1 receptor (Sailer & Salama, 1993). It has no affinity for M1 receptors although it has been reported to have a selective influence on the limbic system (Tandon et al., 1999). Dosage guidelines suggest an optimal dosage to be between 300 to 400 mg daily (BNF).

In terms of clinical efficacy quetiapine has been shown to be indistinguishable from typical antipsychotics in its influence on positive and negative symptoms, although it is superior in terms of its side effect liability, having placebo level extra pyramidal side effects throughout the dosage range. It is also indistinguishable from clozapine, risperidone and olanzapine in terms of its therapeutic effects (Tuunainen et al. 2002).

Previous investigation of the cognitive effects of quetiapine have revealed positive effects on attention (Kopala et al. 2001; Meltzer & Lee, 2001; Stip & Lussier, 1996; Sax et al., 1998), verbal fluency and verbal memory (Velligan et al. 2001; Kopala et al. 2001; Meltzer & Lee
as well as executive function (Kopala et al. 2001). However, performance on the WCST, the Stroop test and on visual memory tests have not been improved by quetiapine treatment (Velligan et al., 2001; Kopala et al., 2001; Meltzer & Lee, 2001).

v) Amisulpride

Amisulpride has a high binding affinity for D2 and D3 receptor subtypes but is devoid of affinity for D1, D4 and D5 receptor subtypes (Sanofi Winthrop LTD, 1997). It has no affinity for serotonergic receptors. Recommended dosage for amisulpride is between 400 – 800 mg daily. Clinical studies indicate that amisulpride is at least as effective as the typical antipsychotics in relieving positive and negative symptoms, but has a reduced side effect profile (Waddington, 2000). In addition, its clinical efficacy is very similar to that of risperidone (Mota et al. 2002).

In terms of cognitive function following amisulpride treatment, some studies have reported an alerting effect with healthy controls (Patat et al. 1999; Grunberger et al. 1989), although negative effects have been reported for semantic reasoning and attention (Ramaekers et al. 1999). Palliere-Martinot et al (1995) reported significant improvements in attentional ability in a group of young drug free schizophrenic patients compared to placebo. This study appears to be the only one that has explored the cognitive effects of amisulpride in a schizophrenic population.

From the preceding discussion a number of issues arise which are worthy of investigation. Firstly, what is the precise role of dopamine and serotonin in the cognitive deficits in schizophrenia? With regard to dopamine, this issue can be explored by comparing the cognitive effects of atypical antipsychotics which block multiple receptors with those which
preferentially block dopamine receptors. Olanzapine, clozapine and quetiapine belong to the former class whilst risperidone and amisulpride belong to the latter class.

With regard to the role of 5HT-2A in cognition, this is open to exploration with a comparison of the cognitive effects of the atypical antipsychotics which have a high affinity for 5HT-2A (risperidone, olanzapine, clozapine) and those which have low or no affinity for 5HT-2A (quetiapine, amisulpride). A summary of the 5HT-2A affinity of the atypical antipsychotics is presented in Figure 1.2 below.

*Figure 1.2 5-HT2A receptor affinity constants for atypical antipsychotics*  

<table>
<thead>
<tr>
<th>Atypical antipsychotic</th>
<th>Affinity constant</th>
<th>Affinity grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>.6</td>
<td>High</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>4</td>
<td>High</td>
</tr>
<tr>
<td>Clozapine</td>
<td>12</td>
<td>High</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>220</td>
<td>Low</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>Infinity</td>
<td>Zero</td>
</tr>
</tbody>
</table>

Another important issue relates to the whether the D2 dissociation speed has any influence on cognition. This has not been previously explored and could be investigated by comparing the cognitive effects of the atypical antipsychotics which have a fast dissociation from the D2 receptor with those which have a slower dissociation. Clozapine, quetiapine and amisulpride belong to the former class whilst olanzapine and risperidone belong to the latter. Finally, perhaps the most important issue that needs investigating is whether there are differences in the cognitive effects of the individual atypical antipsychotics. This issue has not been comprehensively investigated before.

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7 Affinity values taken from Keefe et al. 1999. The lower the affinity constant the more tighter is the receptor binding, hence greater affinity.
1.6 Summary of introduction

The study of cognitive function in schizophrenia is crucial to our understanding of the disorder and may help in the development of more effective treatments. Numerous studies have indicated that aspects of cognition involving memory, attention and executive function are disproportionately impaired in schizophrenia, and these impairments involve pathology of the prefrontal cortex. Atypical antipsychotics have been shown to remediate some aspects of cognition in schizophrenia, although previous studies have been few in number and methodologically limited. In addition, the neurochemical basis of their proposed cognitive effects are not well understood, and may involve dopamine receptors, serotonin receptors, or a combination of both. Furthermore, a recent hypothesis that antipsychotic medications exert their therapeutic effect through fast dissociation from the D2 receptor will be explored to see if D2 dissociation speed has an influence on the remediation of cognitive function. It is also plausible that individual atypical antipsychotics differ in their cognitive effects due to their individual neurochemical profiles.

1.7 Research objectives

1) To explore the cognitive deficits in schizophrenia.

2) To investigate the differential effects on cognition of typical and atypical antipsychotics.

3) To investigate the differential effects on cognition of atypical antipsychotics which have an affinity for multiple receptors (olanzapine, clozapine, quetiapine) and those which have preferential affinity for dopamine receptors (risperidone, amisulpride).
4) To investigate the differential effects on cognition of atypical antipsychotics which have a high affinity for 5HT-2A receptors (risperidone, olanzapine, clozapine) and those which have a low (or no) affinity for 5HT-2A receptors (quetiapine, amisulpride).

5) To investigate the differential effects on cognition of atypical antipsychotics which have a fast D2 dissociation speed (clozapine, quetiapine, amisulpride) and those which have a slower D2 dissociation speed (olanzapine, risperidone).

6) To compare the cognitive effects of the individual atypical antipsychotics.
Chapter 2. Materials and Methods

2.1 Summary and evaluation of the clinical measures used.

i) Brief Psychiatric Rating Scale (BPRS; Overall and Gorman, 1962)

This scale was originally developed in order to provide a quick assessment of psychopathological change in psychiatric patients undergoing treatment, whilst incorporating a thorough description of the main symptom characteristics. Its use has since extended to include the examination and evaluation of psychiatric diagnosis, the classification of psychiatric illness and core symptomology, and the development of clinical predictive models to assess optimum treatment regimes (Hedlund & Vieweg, 1980). The scale contains 18 items covering the following symptoms; somatic concern, anxiety, emotional withdrawal, conceptual disorganisation, guilt feelings, tension, mannerisms and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behaviour, motor retardation, uncooperativeness, unusual thought content, blunted or inappropriate effect, elation or euphoria, and psychomotor excitation. Each item is scored on a 7 item scale between 0 (not present), to 6 (extremely severe), with the interceding items representing increasing degrees of symptom severity (1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe). The ratings on each individual item are summed in order to give a total pathology score, although the scale does permit the classification of symptom scores into distinct subgroups; thinking disturbance, withdrawal / retardation, hostility / suspiciousness, and anxious / depressed (Overall, 1976).

8 The original scale only contained 16 items but in an attempt to make the scale more useful for classification research, items 17 and 18 (elation and psychomotor excitation) were added in 1966.
Psychometric properties

The inter-rater reliability of the BPRS has been investigated many times and most studies report coefficients of .80 or greater for total pathology score (e.g., Steer, 1974). In addition, inter rater reliability coefficients have been reported to be high for each one of Overall's four symptom subgroups (thinking disturbance - .95, withdrawal / retardation - .87, hostility / suspiciousness - .94, anxious / depressed - .94; Hedlund & Vieweg, 1980).

The BPRS has also proved successful at measuring change in patient populations undergoing treatment (e.g., Guy, 1976). In these studies, changes in symptom ratings on the BPRS were confirmed by other clinical measures of symptom change carried out concurrently. These findings suggest that the BPRS has strong properties of both construct validity (because the scale was originally designed as a measure of change) and concurrent validity. Indeed, comparisons of symptom ratings of the BPRS and the Multidimensional Scale for Rating Psychiatric Patients (MSRPP) yielded correlation coefficients of .93 which confirm strong concurrent validity for this scale (Gorham & Overall, 1960). Well replicated factor analytic studies have confirmed the construct validity of the BPRS, with factor structure showing remarkable consistency across a wide variety of patient groups and clinical environments (e.g., Overall et al., 1967; Bonato et al. 1970; Overall and Klett, 1972). In these studies the factor structure was repeatedly found to involve 5 factors (thinking disorder, withdrawal / retardation, anxious / depression, hostility / suspiciousness, psychomotor activation). In summary, the BPRS is a well constructed and well validated scale which is ideally suited for research into symptom changes associated with antipsychotic medication.
ii) Hamilton Depression Scale (HDS; Hamilton, 1969)

The Hamilton Depression Scale provides an assessment of the severity of depression, incorporating an assessment of the cognitive, behavioural and somatic features of the illness. It is the most widely used scale used in studies of depression (Freemantle et al, 1993), but, as with other depression scales, it cannot be used to diagnose depression, only to detail its severity (Bowling, 1995). The scale contains items covering depressed mood, feelings of guilt, suicidal ideation, ability to engage in work and activities, insomnia, anxiety, insight, retardation, agitation, gastrointestinal symptoms, general somatic symptoms, sexual symptoms, hypochondriasis and weight loss. The scale has 21 items in total and each item is scored on a scale of either 3 or 5 points. The 5 point scale covers the following ratings of severity; 0=absent, 1=mild, 2-3=moderate, 4=severe. The three point scale covers; 0= absent, 1= slight or doubtful, 2= clearly present. Scoring is out of 50, although some studies double the score, or have 2 independent raters assess a patient so that the total score is out of 100.

Psychometric properties

Inter-rater reliability has repeatedly been found to be high; 0.84-0.90 (Hamilton, 1970, 1976), 0.88—0.98 (Bech et al. 1975) and 0.94 (Knesevich et al, 1977), as have construct validity, discriminant validity and concurrent validity (Potts et al.1990). Indeed, a correlation coefficient of .70 has been reported between the HDS and the Beck Depression Inventory (Hamilton, 1976). Potts et al (1990) also report that the HDS has a high degree of scale reliability and is sensitive to changes in treatment. Factor analytic studies have proved less impressive with a factor structure having a weak relationship to clinical practice (Hamilton, 1960; 1967). However, factor analyses have been successful in isolating general severity as a dominant factor (e.g., Hedlund and Vieweg, 1979), and so this scale can be considered suitable for use in the current study.
2.2 A summary and evaluation of the cognitive measures used

The cognitive measures used in this study were chosen on the basis that they assessed aspects of cognition that have previously been reported to be impaired in schizophrenia. In addition, premorbid estimations of I.Q. were taken and a screening test for global cognitive impairment was also included.

i) National Adult Reading Test (NART; Nelson, 1982)

The NART provides a measure of premorbid intellectual functioning by assessing the ability of a subject to pronounce irregularly spelled words such as ‘debt, gaol, leviathan’. The test was developed on the basis of findings which indicate that firstly, vocabulary has a high correlation with overall intellectual ability, and secondly that vocabulary has a strong resistance to the dementing process. Taken together, these factors suggest that a patient’s vocabulary may provide a good indication of premorbid intellectual ability. More specifically, Nelson & O’Connell (1978) suggest that the ability to correctly pronounce a word provides an indication of premorbid familiarity with that word, and therefore testing this ability could be used to provide an indication of premorbid intelligence. However, patients with dementia can pronounce unfamiliar but regularly spelled words without difficulty (Lezak, 1995), which may give the false impression that they have larger vocabularies than they actually have. To avoid this problem, Nelson & O’Connell (1978) suggest that testing the pronunciation of phonetically irregular words, i.e., words which do not follow the normal grapheme-phoneme rules, is a better method of assessing premorbid vocabulary because these words can only be pronounced correctly by someone who has previously been exposed to them in spoken form.

The NART consists of 50 phonetically irregular words, presented individually on white card, which the patient has to read out aloud. A point is given for each correct pronunciation, and
the number of mispronunciations are recorded. After completion of the test the number of errors made are compared to standardised norms which provide an indication of premorbid I.Q level.

Psychometric Properties

The psychometric properties of the NART are impressive, making it amongst one of the most reliable tests used in clinical practice (Crawford, 1992). It boasts a high split half reliability coefficient of .90 (Crawford et al., 1988), a test-retest reliability coefficient of .98 and an inter-rater reliability coefficient of between .96 and .98 (Crawford et al., 1989a). The construct validity of the NART as a measure of intelligence was assessed in a factor analytic study of the WAIS and NART (Crawford et al., 1989). The NART error score was found to load very highly on verbal intelligence (.85) and a subsequent study has reported that NART performance predicted 66% and 72% of the variance on the WAIS full scale I.Q and verbal I.Q respectively (Crawford et al., 1989a). However, the NART was somewhat poorer at predicting performance I.Q on the WAIS (33%).

The clinical use of the NART has proved successful in both neurological and psychiatric populations. For example, Nelson & O'Connell (1978) compared the NART and WAIS performance of 40 patients with cortical atrophy. Although the group were significantly impaired on the WAIS compared to the NART standardisation sample, there was no significant difference in NART performance. Similarly, O'Carroll et al (1987) tested a group of dementing patients with the NART and then re-tested them a year later. NART performance remained unchanged despite an increase in dementia severity and physical disability. Many studies have since confirmed that NART performance is largely unaffected by a wide range of disorders, including; alcoholic dementia and closed head injury (Crawford et al. 1988a); dementia of Alzheimer type (e.g., O'Carroll et al, 1987); depression (Crawford
et al. 1987); Parkinson's disease (e.g., Lees & Smith, 1983); and schizophrenia (Crawford et al. 1992).

ii) The Mini-Mental State Examination (MMSE; Folstein et al, 1975)

This test is widely used as a brief screening instrument for clinically significant cognitive impairment. Consisting of 11 short questions, it tests the following cognitive abilities; orientation, registration, attention, calculation, recall, language functioning and praxis. The maximum score on this test is 30 and scores falling below 24 are considered indicative of clinically significant cognitive impairment, although several authors have suggested higher cut off scores for specific disorders (e.g., 25 for well educated patients with Alzheimer's disease (Galasko et al, 1990), 27 for multiple sclerosis patients (Beaty & Goodkin, 1990). Indeed, Bleecker et al (1988) recommend differential cut off points for different age ranges; 29 for people aged 40-49, 28 for 50-79 year olds, and 26 for 80-89 year olds.

Psychometric properties

High test-re test reliability has been demonstrated in the original standardisation study either when the examiner is the same (.89) or different (.83) (Folstein et al, 1975). This finding has since been replicated (Dick et al, 1984). Factor analytic studies have emphasised the role verbal abilities, comprehension, memory and attention play in MMSE performance (Giordani et al., 1990; Zillmer et al., 1990; Morris et al., 1989). In terms of construct validity, the MMSE has had most success at discriminating between patients with moderate or severe impairments and control subjects (e.g., Filley et al. 1989). Less success has been reported in distinguishing mildly impaired patients (e.g., Knight, 1992a) or patients with focal or lateralised lesions (Schwamm et al., 1987; Naugle & Kawczak, 1989) from control subjects. However, the MMSE is sensitive to the progressive cognitive decline in dementia (Morris et al., 1989; Schmitt et al., 1989) and has had success at distinguishing between the performance
profile of Huntington's patients (Tanahashi et al., 1985), Alzheimer's patients (Brandt et al., 1988) and multiple sclerosis patients (e.g., Beatty & Goodkin, 1990). As a tool to screen for dementia or cognitive impairment the MMSE is more than adequate.

iii) Graded Naming Test (GNT; McKenna & Warrington, 1983)

The Graded Naming Test (GNT) provides a means of investigating language impairment or deficits in semantic memory through the assessment of a subject's ability to name a series of inanimate objects when presented with their pictures. The test consists of 30 line drawings which are graded in difficulty in order to take into account individual differences in naming vocabulary. For example, easier items, such as 'kangaroo, screwdriver, corkscrew', can be successfully named by more than 90% of the normal population, whereas more difficult items, such as 'centaur, tutu, retort', can be successfully named by less than 30% of the normal population.

As naming ability correlates highly with measures of verbal intelligence (e.g., McKenna & Warrington, 1980) the GNT can be used to provide a measure of premorbid I.Q. in a similar way to the NART. More importantly, the association between naming ability and intelligence permits comparisons to be made between performance on the GNT and other measures of intelligence, with large discrepancies in the scoring between the respective I.Q. estimations indicating decline and perhaps pathology. For example, low scoring on the GNT compared to high scoring on other measures of intelligence may indicate a language impairment or a degradation in lexical knowledge. Another indication of impaired performance on the GNT can be obtained by comparing the results with other clinical variables in a particular individual. For example, patients with temporal lesions are significantly impaired in object naming tasks compared to patients with either parietal or frontal lesions (McKenna & Warrington, 1983). A patient with a low score on the GNT who also presented with visual hallucinations or inappropriate emotional responses may indeed fit the picture of someone
with a temporal lesion. More recently the GNT has been used to investigate semantic memory deficits in patients with schizophrenia (e.g., Laws et al. 2000) because performance on this test reflects the integrity of the semantic store or 'mental thesaurus'.

Psychometric properties

The GNT was standardised on 100 subjects with an age range between 20 and 76. From an initial total of 61 line drawings, 30 were chosen as being appropriate for inclusion in the test and drawings that were too easy or too difficult to produce good discrimination were excluded. Items were rated in order of difficulty on the basis of how many people could successfully name them. The standardisation study confirmed the association between the GNT and measures of intelligence (NART = .73, Schonell Graded Word Reading Test = .69, WAIS vocabulary subtest = .72). In order to validate the GNT on a patient population with language difficulties, McKenna & Warrington (1983) gave the test to 46 patients with unilateral left hemisphere lesions. Results of this study confirmed that the test was sensitive enough to detect minor degrees of naming difficulty, and interestingly, a comparison of scores between the patient group and control sample revealed quantitative, not qualitative differences. On the whole, the patient population scored about 30% lower correct responses on all items in the test. No data are available on either the test re-test reliability or inter-rater reliability of the GNT, although it can be assumed that given the simplicity of this test these properties would be adequate.

iv) The Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn & Baddeley, 1985)

This test was developed for the purpose of providing an ecologically valid assessment of memory impairment. Traditional memory tests, although being adequate at measuring the acquisition and retention of experimental stimuli, do not provide an indication as to how a
memory impairment may affect a person’s ability to function in everyday life. For example, the Recognition Memory Test (Warrington, 1984) requires a subject to remember 50 faces and 50 words, but does not specify how the acquisition and retrieval of these items relates to the everyday memory problems a person with an impairment may encounter. The Rivermead Behavioural Memory Test overcomes these problems of ecological validity by assessing a patient’s memory in a naturalistic setting using naturalistic tasks. The test comprises a number of subtests:

- Remembering a name (given the photograph of a face)
- Remembering a belonging (a belonging of the subject is concealed and the subject has to remember to ask for it back at the end of the session).
- Remembering a message after a delay (The subject is told to say some key words when an alarm rings after 20 minutes).
- An object recognition task (ten pictures of objects are shown, and the subject then has to recognise these out of a set of 20 pictures shown after a delay).
- A face recognition task (similar to object recognition, but using five faces to be recognised amongst five distracters)
- A task requiring the subject to remember and follow a route around the room both immediately and after a delay.
- Delivering a message – whilst retracing the route around the room the subject has to remember to place a message envelope in a specific place.
- Recall of a short story both immediately and after a delay
- Orientation and date questions

The test has four parallel versions and so is suitable for assessing change in memory function over time with little influence of practice effects. Each test is scored according to two criteria; a screening score which represents a simple pass / fail score (0 or 1) with a range between 0 – 12, and a standardised profile score which categorises performance on each test.
as either impaired (0), borderline (1) or normal (2). The standardised profile scoring range is between 0-24. The inclusion of the standardised profile score is necessary in order to provide a wider range of scores, which would allow for the detection of subtle differences between levels of memory function and reduce ceiling effects. The levels of memory function indicated by each scoring criteria are as shown in Figure 2.1 below.

Figure 2.1 Scoring criteria on the Rivermead Behavioural Memory test

<table>
<thead>
<tr>
<th>Level of Memory Function</th>
<th>Screening Score</th>
<th>Profile Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10, 11, 12</td>
<td>22, 23, 24</td>
</tr>
<tr>
<td>Poor Memory</td>
<td>7, 8, 9</td>
<td>17 – 21</td>
</tr>
<tr>
<td>Moderately Impaired</td>
<td>3, 4, 5, 6</td>
<td>10 – 16</td>
</tr>
<tr>
<td>Severely Impaired</td>
<td>0, 1, 2</td>
<td>0 – 9</td>
</tr>
</tbody>
</table>

Psychometric properties

The RBMT was validated on 176 brain damaged patients and 118 control subjects. Both inter-rater reliability (100%) and parallel form reliability (in the range of .83 to .88 for the profile score) suggest strong psychometric properties. Strong correlations were also reported between the recorded memory errors of patients with brain injury, and both the profile score (-.75), and screening score (-.71). RBMT scores for this group of patients was also significantly correlated with performance on a variety of other memory and learning tests (Wilson et al. 1989), a finding that has been replicated (e.g., Malec et al. 1990). More recently the RBMT has been used to investigate the memory deficits associated with schizophrenia (e.g., Mockler et al. 1997).
v) Digit span test

This test measures the span of immediate verbal recall although it is a matter of debate whether this test is primarily a measure of attention (e.g., Lezak 1995; Kaufman et al, 1991) rather than a test of immediate memory (Goldberg et al. 1998). The task of the subject is simply to repeat a number sequence given by the examiner, such as 6-1-4. Each digit is pronounced at the rate of 1 per second to minimise the use of chunking to aid recall. The subject is usually given two chances at repeating the same sequence of digits, although Lezak (1995), sometimes administers the same string three times if she suspects that failure to repeat the sequence is due to distraction or non co-operation, rather than a failure of attentional or memory processes. If the subject correctly repeats a sequence of digits then the examiner gives a longer sequence of digits for the subject to repeat. The length of each number string is usually increased by 1 digit following a correct repetition. The test is stopped when the subject reaches their limit of immediate recall and cannot successfully repeat the number string. Usually this happens around the 7 digit mark, indeed Kaplan et al. (1991) reported that 89% of a large sample of controls had spans of between 5 and 8 digits.

Psychometric Properties

The test re-test reliability of the digit span test has been reported to be between .66 and .89, although practice effects, the subjects' age and the interval latency have influenced the correlation coefficients in some studies (Matarazzo and Herman, 1984; Snow et al, 1989; Youngjohn et al., 1992). Neuropsychological findings indicate that digit repetition is susceptible to left hemisphere damage, but is left largely unaffected by either right hemisphere or diffuse damage (Black, 1986; Horn and Reitan, 1984; Newcombe, 1969; Risse et al., 1984; Weinberg et al., 1972). Head trauma or psychosurgery do reduce digit span performance temporarily, but recovery is likely within a few years (e.g., Lezak, 1979). In addition, although the digit span test is insensitive to dementia in the mild stage, once into the
moderate and severe stages performance can be seen to decline dramatically (e.g., Botwinick et al. 1986).

vi) The Cambridge Automated Neuropsychological Testing Battery (CANTAB)⁹; CeNeS Cognition Ltd.

As the CANTAB is a comparatively new battery of tests which have been seldom used to investigate cognition in schizophrenic populations, each subtest will be described in some detail.

Motor Screening

Subjects are required to respond to a series of flashing crosses which appear at random locations on the computer screen. In order to deactivate a cross, the subject is required to touch it as soon as it appears. Following a 6 second delay another cross appears, and a total of 10 crosses are presented in each trial. Success on this task indicates that subjects do not have any psychomotor difficulties which might affect performance on other tasks within the CANTAB battery.

Pattern Recognition

This is a test of pattern recognition memory comprising 2 stages, a presentation stage and a recognition stage. In the presentation stage of the test a series of 12 coloured, random patterns are presented one at a time in the centre of the screen (see Figure 2.2). These patterns were constructed so that verbal labels could not be easily attached to them. The subject is asked to try to remember the patterns that they see. Following completion of the presentation stage of

⁹ The CANTAB original version (1.86) was replaced during the study by CANTAB2 (version 2.35) although this version contained identical tests to the original CANTAB
the task there is a several second delay. In the recognition stage of the test the subject is presented with 12 pairs of coloured patterns presented successively. One pattern within each pair is one that had appeared in the presentation stage of the test, the other pattern within the pair is novel. Subjects are required to touch the pattern which they recognise as having been presented in the initial stage of the test. Visual feedback of recognition accuracy is given in the form of a green tick or a red cross which appears on the screen immediately after the subject has made a response. After 12 pairs of patterns have been presented to the subject the whole process is repeated with 12 new patterns for the subject to remember. Recognition scores for the whole set of 24 patterns is converted to a percentage of the correct total responses made.

*Figure 2.2. CANTAB test of pattern recognition. The subject is shown a series of shapes which they subsequently have to pick out from distracters.*

Spatial Recognition

This is a test of spatial recognition memory and like the pattern recognition test it contains a presentation stage and a recognition stage. In the presentation stage the subject is shown a series of white squares appearing one after the other at random locations on the screen (see
Figure 2.3). The squares are presented for a period of 3 seconds and after completion of the presentation stage there is a several second delay. In the recognition stage of the test the subject is presented with a series of pairs of white squares. One square within the pair appears in the same location as a square that had been seen in the presentation stage of the test, the other square appears in a novel location. The subject has to pick out the square that appears in a location previously seen in the presentation part of the test. Visual feedback on the accuracy of choice is given using red crosses and green ticks. A total of 4 sets of 5 targets are presented to the subject, and scores are converted to a percentage of total correct responses made, i.e., 20.

Figure 2.3 CANTAB test of spatial recognition. The subject is required to remember the locations of boxes on the computer screen.

Intra Dimensional / Extra Dimensional Shift (ID / ED)

This test is a computer analogue of the Wisconsin Card Sorting Test (WCST) and like its traditional counterpart it assesses the ability of the subject to shift attentional set. Initially, the subject is presented with two simple coloured shapes, each appearing randomly in one of four possible locations. The subject is then given the following instructions:
'Now you can see two patterns. One of the patterns is correct and the other is wrong. What
you have to do is touch the one you think is correct. There is a rule that you can learn and
follow to make sure you get it correct each time. The computer will be keeping track of how
you are doing and when it is clear that you know the rule, the computer will change it, but
remember, this will not happen very often. When the rule is changed you will have to think of
a different rule in order to go on doing well. To begin with, there is nothing on the screen to
tell you which of the two patterns is correct so your first choice will be a simple guess.
However, the computer will give a message after each attempt to tell you whether you are
right or wrong’ (CeNeS Cognition Ltd, 1998, p22)

Following these instructions the subject is requested to start the test by making their choice as
to which shape is correct. Visual feedback in the form of a red cross or a green tick indicates
whether the subject’s choice was correct or incorrect. Once the subject knows and chooses the
correct shape on 6 successive occasions it is assumed that they have learnt the rule.
Subsequently, the criterion changes and the rule is changed so that the previously incorrect
shape becomes correct shape and the previously correct shape becomes the incorrect shape.

Once the subject has learnt this simple shape discrimination and reversal, another dimension
is added. Here, variously shaped lines are introduced which firstly are presented adjacent to
the shapes, but later are presented superimposed on the shapes (see Figure 2.4). Initially, the
lines are irrelevant to the task but when the irrelevance of the lines has been established, one
of two distinct types of shift occurs. Firstly, an intra-dimensional shift occurs whereby new
shapes are presented but the shapes are still the relevant dimension. After the subject has
learnt the discriminative rule with the novel shapes, an extra-dimensional shift occurs where
the lines finally become relevant and the previously trained shape becomes irrelevant.

The different stages of the test can be test can be defined as follows:

1) Simple discrimination – subject has merely to choose, and continue choosing, the correct
shape from a possible two shapes.
2) Simple reversal - the shape that was previously correct now becomes incorrect and the subject has to reverse his responses to continue doing well.

3) Compound discrimination adjacent – lines are introduced adjacent to the shape but the shape is still the relevant dimension.

4) Compound discrimination superimposed – lines are superimposed onto the shapes but the shape is still the relevant dimension,

5) Compound reversal - the shape that was previously correct now becomes incorrect and the subject has to change his response to continue being correct.

6) Intra dimensional shift - novel shape and line stimuli are introduced to replace the old stimuli but shape is still the relevant dimension.

7) Intra dimensional shift reversal - The novel shape that was previously correct now becomes incorrect and the subject has to adjust their responses.

8) Extra dimensional shift – the lines finally become relevant and the shapes become irrelevant.

9) Extra dimensional shift reversal – the correct line now becomes incorrect and the subject has to reverse their responses.

Scoring on this test is in terms of number of stages reached (1 – 9), total errors – subjects failing to adjust responses when the relevant shape / dimension is changed, errors at extra-dimensional shift, and errors up to extra dimensional shift. Errors at the extra dimensional shift stage are considered equivalent to the category shift in the Wisconsin Card Sorting Test and are therefore considered the key indicator of attentional set shifting ability on this test (Fray et al, 1996).
Figure 2.4. CANTAB test of attentional set shifting ability - compound discrimination superimposed (stage 4). The shape dimension continues to be correct but the lines are superimposed to act as distracters. Later, the lines become the relevant dimension and the shapes become irrelevant to the task.

Spatial Working Memory

In the training stage of this test the subject is presented with 3 red boxes on the computer screen. The subject is required to search these boxes, by touching them, in order to locate blue counters that are hidden inside them. When a box has been touched it briefly 'opens' to display either a blue token or nothing, and then closes again. Once a token has been found inside a particular box, the subject has to transfer the token to ‘home base’, an area to the right hand side of the screen which provides a visual representation of how many tokens have been found and how many are left to find (see Figure 2.5). Following the discovery of a token in a particular box, that box would not be used again to hide a new token and the subject must try to remember not to return to boxes that have already been searched. The subject has to continue searching for blue tokens until enough tokens have been found to fill ‘home base’. There are twelve trials on this test, following the training trials with 3 boxes, there are 4 trials with 4 boxes, 4 with 6 boxes and 4 with 8 boxes.
The main type of error that is recorded on this test is a *between-search error* when the subject returns to a box where a token has been previously found. In addition, a score representing the strategy used to complete the task is also recorded. An optimum strategy would be for the subjects to follow a pre-planned search sequence, starting with one box and returning to that box at the beginning of a new search after a token has been found. A high strategy score would be obtained if the patient used the same starting location for the search within each of the six and eight box problem. A low score represents random starting positions for each search. The range of strategy score is between 1 (optimum) and 37 (very poor).

*Figure 2.5 CANTAB test of spatial working memory. The subject must systematically search for blue counters hidden inside red boxes whilst remembering not to search the same box twice.*
Spatial Span

This test involves the subject observing a sequence of squares changing colour, and then touching the squares in the same order in which they had changed colour. To begin with, 2 boxes change colour but this number is incrementally increased to a maximum of 9. Scoring on this test is in terms of the maximum sequence of squares changing colour (between 2 and 9) that the subject could successfully follow. Figure 2.6 displays this test.

Figure 2.6 CANTAB test of spatial span. The subject must observe and follow a series of boxes changing colour.

Stockings of Cambridge

This test is based upon the Tower of London planning test where the subject is required to change the position of coloured balls on pegs to match a predefined pattern. On the CANTAB version of this test the computer screen shows two displays which are meant to represent coloured balls that are suspended in stockings hanging from a beam (see Figure 2.7). The bottom display represents the starting point for each trial and is the part of the display that the subject can manipulate. The top display represents the target display which the subject has to
match. The subject is required to move the coloured balls in the bottom display to match the
target arrangement at the top of screen. However, only one ball can be moved at a time and
balls cannot be moved if they are underneath another ball. There is also a limit to the number
of places where each ball can be moved to. These constraints mean that for some trials the
subject has to achieve several sub goals, in terms of ball positioning, whilst keeping in mind
the main goal. For example, one of the trials may have a target display showing 3 balls in the
same stocking, with the red ball on top of the green ball and the green ball on top of the blue
ball. If the starting point for this trial has the three balls in the same stocking but the opposite
way around, i.e., red ball at the bottom of the stocking, then the blue ball and then the green
ball, then to match the target display the subject would have to move all three balls from this
stocking (a sub goal) before replacing them in the stocking in the correct order (the main
goal). The number of moves the subject has to make to match the target sequence begins with
1, as a training exercise, and then increases to 2, 4 and finally 5 moves. There are 12 problems
in total on this test. In order to calculate thinking time for each stage of the task, a procedure
that controls for motor performance is inserted at two intervals during the test. Here, the
computer moves one ball at a time in the upper display, mimicking the movements made by
the subject in the corresponding planning phase. The subject must follow this sequence by
moving the balls in the lower display. These yoked control tasks repeat every move made by
the subject and therefore allow by subtraction, estimates of planning and thinking time for
each stage of the task independently of movement time.

This test is scored in terms of;

1) number of problems solved within the minimum number of moves (up to 12)
2) initial thinking time for each problem—the time taken to make the first move after the
   presentation of the display
3) subsequent thinking time for each problem—the time spent thinking about a problem
during its execution.
However, Elliot et al (1998) suggests that there can be three additional measures of performance on this task; percentage of problems solved perfectly at each level of problem difficulty, mean number of moves made above the ideal minimum, percentage of problems solved within the maximum possible number of moves.

Figure 2.7 CANTAB Stockings of Cambridge test. The subject has to move the coloured balls in the bottom half of the screen to match a target pattern in the top half of the screen.

Psychometric properties of the CANTAB

*Construct validity* - It would be reasonable to assume that construct validity is adequate for the CANTAB on a cognitive level because the test it is based on traditional measures of cognitive function which have well validated psychometric properties. Indeed all the CANTAB tests used in the current study are analogous to more traditional tests of cognitive function, for example, the Stockings of Cambridge test is a computer version of the Tower of London. In addition, the CANTAB can be considered to have strong construct validity on a neurophysiological level because the battery was constructed on the basis of animal work.
where the relationship between sub test scores and specific brain regions have been well established.

*Inter-rater reliability* - There is no data available on the inter-rater reliability of the CANTAB. However, when one considers that each test is automated with no tester input once a trial has begun, and that instructions and prompts given to the subject are standardised, it can be assumed that inter-rater reliability is adequate.

*Discriminant validity* - The CANTAB has had considerable success in delineating the cognitive profiles of different patient groups and can therefore be considered to have good discriminant validity. Distinct cognitive profiles on the CANTAB battery have been reported for patients with neuro-degenerative diseases (Alzheimer's disease; Sahgal et al., 1991: frontal dementia; Coull et al., 1996: Parkinson's disease; Owen et al. 1993a, 1993b: Huntington's disease; Lange et al., 1995), psychiatric disorders (depression; Elliott et al., 1996: schizophrenia; Elliott et al., 1995) and deficits following neurosurgical lesions (Owen et al., 1990; 1991; 1995).

*Concurrent validity* - No studies have yet explored the concurrent validity of the CANTAB battery of tests although it can tentatively be assumed that given the similarity of the tests to conventional measures of cognitive function, this property would be adequate.

*Test-retest reliability* - Coolican (1998) suggests that test / re-test correlations for neuropsychological tests should yield correlation coefficients of at least 0.75 to 0.80. To date only two studies have examined correlation coefficients for the CANTAB battery of tests and these are displayed in Figure 2.8.

According to the Coolican criteria, only the Pattern Recognition test (.72, .84) and the stage reached component of the ID/ED task (.75) have acceptable 'r' levels. However, correlation
coefficients for the between search errors on the Spatial Working Memory test (.70, 68) and the errors to ED shift on the ID/ED set shifting task (.70) are close to the Coolican criteria and can be considered acceptable. Furthermore, correlation coefficients for the spatial span task (.60, .64) and for several performance indices on the Stockings of Cambridge test (Mean initial think times: .69; Mean subsequent think times: .64; Minimum move solutions: .64, 60) are approaching criteria levels. Indeed, these figures are in the same range or higher than correlation coefficients reported for traditional tests of executive function such as the WCST (between .26 and .49; Paolo et al., 1996), the Stroop test (between .22 and .53; Lowe & Rabbitt, 1998) and verbal fluency tasks (.71; Snow et al. 1988), which suggests that the correlation coefficients of the CANTAB measures of executive function are at least as high as they can be for this type of test.

**Figure 2.8. Test re-test correlations (Pearson's R) of the CANTAB in two studies.**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Pattern Recognition % correct</td>
<td>.72</td>
<td>.84</td>
</tr>
<tr>
<td>Spatial Recognition % correct</td>
<td>.48</td>
<td>.57</td>
</tr>
<tr>
<td>Spatial Span</td>
<td>.60</td>
<td>.64</td>
</tr>
<tr>
<td>Spatial Working Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy score</td>
<td>.63</td>
<td>-</td>
</tr>
<tr>
<td>Between search errors</td>
<td>.70</td>
<td>.68</td>
</tr>
<tr>
<td>ID/ED set shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage reached</td>
<td>.75*</td>
<td>-</td>
</tr>
<tr>
<td>Total errors</td>
<td>.40*</td>
<td>-</td>
</tr>
<tr>
<td>Errors to ID shift</td>
<td>-</td>
<td>.09</td>
</tr>
<tr>
<td>Errors to ED shift</td>
<td>-</td>
<td>.70</td>
</tr>
<tr>
<td>Errors at ED shift</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stockings of Cambridge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum move solutions</td>
<td>.64</td>
<td>.60</td>
</tr>
<tr>
<td>Mean initial think time (all problems)</td>
<td>.69</td>
<td>-</td>
</tr>
<tr>
<td>Mean subsequent think time (all problems)</td>
<td>.64*</td>
<td>-</td>
</tr>
<tr>
<td>Average number of moves - 4- move problem</td>
<td>-</td>
<td>.26</td>
</tr>
<tr>
<td>Average number of moves - 5- move problem</td>
<td>-</td>
<td>.47</td>
</tr>
</tbody>
</table>

* denotes Spearman Rho calculations

Lowe & Rabbitt (1998) suggest that test re-test reliability is low for tests of executive function because this type of test work only when they are novel, and that once the subject learns the optimal strategy then performance can increase dramatically. However, if the
subject fails to learn the strategy, then performance will not improve to any great extent. Therefore, due to the ‘either you get it or you don’t’ nature of executive tests, test re-test reliability will be low. In contrast, tests that allow for gradual improvements in performance will be much more reliable.

Only the spatial recognition test yields correlation coefficients that are unacceptably low (.48, .57), the reasons for which are unclear. Neither study reported correlation coefficients for initial and subsequent thinking time for each separate problem on the Stockings of Cambridge test, nor for the errors at the ED shift stage of the ID/ED test. This latter omission is surprising because it is this stage of the task that provides the crucial measure of a subject’s set shifting ability and therefore can be considered the most important part of the test (Fray et al. 1996).

Clearly more investigation of the test-retest reliability of the CANTAB tests is needed, covering all the sub-tests within each battery and using a large normal sample of controls. Indeed, the validation sample used by Lowe & Rabbitt (1998) were between the ages of 60 to 80 (mean 70) and therefore can not be considered the ideal sample with which to validate any new measure of cognitive function for use with the general population or with clinical populations of a younger age range. Tests relying on fluid intelligence, the ability to reason and problem solve in the absence of familiar solutions, do show age related decline (e.g., Kaufman et al. 1989) and therefore it could be argued that low test re-test reliability reported in the Lowe & Rabbitt study reflects changes in the cognitive profile of the sample used as much as it reflects the psychometric properties of the CANTAB.

In addition to describing the CANTAB battery of tests and detailing its psychometric properties, it is also useful to note some other features of this battery of tests which make it arguably superior to conventional measures of cognitive functioning.
Advantages of CANTAB over traditional tests of cognitive function.

*Conceptually driven* - The tests incorporated in the CANTAB battery were adapted for human use from animal models of cognitive function which have been well validated. Extensive data are available on the relationship between scores on sub-tests and very specific areas of brain damage which means that inferences as to the neurophysiological basis of cognitive impairment can be made reliably (Fray et al., 1996). For example, performance on the spatial working memory test is impaired after frontal lobe damage (Owen et al. 1990), whereas the pattern recognition memory test is sensitive to lesions of the temporal lobe (Owen et al. 1995). More traditional tests of cognitive function have tended to be selected on the basis of informed intuitions or clinical tradition (Lowe & Rabbitt, 1998), and so have not offered as coherent an account of neuropathological changes associated with test performance as the CANTAB battery.

*Greater accuracy and in depth assessment* - The CANTAB is able to provide more accurate measures of cognitive ability than conventional pencil and paper tests. Reaction times, and the time taken to complete tasks can be measured to the nearest millisecond, and other performance indices can be taken concurrently, such as accuracy and efficiency. For example, the Stockings of Cambridge Task is able to provide millisecond measurements of thinking time prior and during the execution of four complex tasks, in addition to providing a score of how accurately each task was completed. The non computerised version of this task, the Tower of London, is only able to measure the patient’s ability to solve the tasks efficiently, with no measurement of latency.

*Selective and sensitive* - The sensitivity and selectivity of the CANTAB has been demonstrated with the construction of cognitive profiles for different patient groups; Alzheimer’s disease (Sahgal et al., 1991), frontal dementia (Coull et al., 1996), Parkinson’s
disease (Owen et al. 1993a, 1993b), Huntington’s disease (Lange et al., 1995), depression (Elliott et al., 1996), schizophrenia (Elliott et al., 1995) and some neurosurgical cases (Owen et al., 1990; 1991; 1995).

An ‘all in one’ battery - The CANTAB battery is able to provide a thorough assessment of an individual’s cognitive functioning because it contains 3 sub-batteries measuring Visual Memory, Attention and Working Memory and Planning respectively. This ‘all in one’ approach is a considerable improvement on traditional batteries which tend to only focus on one aspect of cognitive function: this meant that to get an all round picture of an individual’s cognitive state, the researcher had to use a number of different tests.

Provides instant feedback - The CANTAB can analyse performance during the execution of a task and therefore provide instant feedback to the subject. Instant, direct feedback has been reported to enhance interest in tasks and thereby increase motivation to perform well (Morris, 1987). This factor may help reduce the motivational difficulties which are a feature of some neuropathological disorders, such as dementia or schizophrenia in its negative phase, which can sometimes confound test scores (Lezak, 1995). However, the flip side to this is that negative feedback following an incorrect response may have a detrimental effect on subsequent performance. Indeed, Elliot et al (1996) found that patients with unipolar depression, having failed to correctly solve one problem, were far less likely than controls to solve subsequent problems correctly.

Avoids floor and ceiling effects - The CANTAB is designed to assess a broad range of cognitive ability thereby avoiding ceiling effects in normals (Coull et al. 1995), and floor effects in elderly impaired patients (Sahakian et al., 1988).
Consistency of presentation - Standardised instructions and uniform presentation of stimuli reduce the problem of conscious or inadvertent influencing of the subject's responses by the tester in the form of verbal comments or changes in gesture or posture (Wilson & McMillan, 1992).

Maintain Interest- CANTAB tests are designed to be visually interesting and aurally attractive (e.g., playing tunes when parts of a test are successfully completed) which may increase interest in the tasks and increase motivation to perform well (Wilson & McMillan, 1992). This makes the battery ideal to use with children, or adults with limited cognitive ability.

Non verbal - CANTAB tests are largely non verbal, using non verbal stimuli and requiring non verbal responses. This means that the tests are largely self-explanatory, reducing the influence of the experimenter, and in some circumstances can be administered without verbal instruction (Fray et al.1996). This makes the CANTAB ideal for use with people with hearing impairments, or for cross cultural studies (e.g., Maruff et al. 1995).

2.3 The sample

i) Patients

Patients with a DSM-IV diagnosis of schizophrenia who were between the ages of 18 and 60 were included in the study. Patients who fulfilled these criteria but who had either a global cognitive deficit, as indicated by their medical history or by achieving a score of <24 on the mini mental state test, or who had had a significant head injury, were excluded from the study. As the purpose of the study was to investigate changes in cognitive function, one patient had had a significant head injury which resulted in a coma for 2 weeks. However, a full recovery was made and the patient re-attended college after the accident. The onset of psychosis did...
associated with atypical antipsychotic medication, baseline measures had to be taken prior to, or shortly after, the patient began this treatment. Therefore, only patients that were about to start, or had recently started, their course of antipsychotic treatment were suitable for the study. A recruitment deadline of 6 weeks from the start date of the antipsychotic medication was set as it is within this period that clinical response is usually observed, and it was considered that within this period any medication related cognitive changes would not have had chance to take effect. The follow up assessments were conducted at 9 months and 18 months post baseline respectively. These time intervals were set in order to get a long term picture of the cognitive changes associated with antipsychotic treatment. Indeed, there is evidence that the cognitive improvements associated with atypical antipsychotics extend over the long term (Mortimer, 2001), and previous studies have been criticised for their short term focus (Keefe et al. 1999). The atypical antipsychotics under investigation were the ones in clinical use in the U.K. at the time of the investigation. These were risperidone, olanzapine, clozapine, quetiapine and amisulpride. In addition, patients were also sought who were beginning a course of treatment with one of the typical antipsychotics to act as a patient control group. The typical antipsychotics in clinical use at the time of the study were chlorpromazine, flupenthixol, pimozide, sulpiride, fluphenazine, haloperidol, trifluoperazine, thioridazine, promazine and lozapine.

ii) Controls

A small group of healthy controls (N=19) who had no history of psychiatric illness or brain injury were also included in the study. These recruits were taken from work colleagues and friends of the investigators and were matched in terms of age, premorbid I.Q. and years of education with the schizophrenic group. It was considered necessary to include a group of healthy controls for two main reasons. Firstly, this allowed statistical comparisons to be made not occur until 5 years after this accident and in addition, cognitive testing for the current study did not reveal any impairment.
between the schizophrenic group as a whole and the controls which would not have been possible using normative published data. Secondly, by including a healthy control group this enables us to distinguish between improvements in performance due to repeat testing or practice effects, and improvements in performance that are due to the action of antipsychotic medication. However, it was only considered necessary to test the controls using the CANTAB as some tests within this battery have been criticised for having low test re-test reliability (e.g., Lowe & Rabbitt, 1998). In addition, there is no CANTAB normative data for the age group used in the current study – 18 to 60. Instead, the CANTAB norms are split into age bands (<35, 35-49, 50-59, 60-69, 70+) or presented as aggregate global norms (including controls over 60). Therefore they are not suitable for comparison with the patients used in the current study. It was not considered necessary to test the controls on the Rivermead Behavioural Memory test because this test has parallel versions for repeat testing and therefore practice effects would not be predicted. Similarly, practice effects would not be expected for the digit span test because of the short term nature of this test and the fact that it has high test re-test reliability. With the Graded Naming Test, stability of the control performance over time would be predicted and therefore this test was also not administered to healthy controls. The controls were tested with the CANTAB over two time periods, separated by a gap of nine months. It was not considered necessary to test the controls three times as they were performing at ceiling level at 9-month-follow-up.

2.4 Procedure

Ethical approval for the study was obtained from the Hull and East Riding Local Research Ethics Committee. In addition, permission to approach patients was granted by Hull and Holderness Community Health NHS Trust.
i) Patient recruitment

All consultant psychiatrists within Hull and East Yorkshire Community Health NHS Trust, and a sample of consultant psychiatrists from North East Lincolnshire and Scunthorpe and Goole NHS trusts, were written to with a summary of the study and a request for assistance in recruiting patients. These letters were followed up with a phone call and if the response from the consultant was positive then a meeting was arranged to provide the consultant with further information about the study protocol and to answer any concerns that they may have had. Once the consultant was happy to assist in recruiting patients for the study, arrangements were made so that a member of the research team would be informed when a patient with schizophrenia was beginning antipsychotic medication for the first time or switching from one antipsychotic to another. At the start of the study it was expected that each consultant psychiatrist would simply inform a member of the research team when one of their patients became suitable for inclusion in the study. However, this did not work out in practice, with only a small number of consultant psychiatrists routinely referring patients for the study. It was felt that this problem was probably due to the large work load of the consultant psychiatrists which limited their time available to directly refer patients for the study. To resolve this problem another meeting was arranged with each individual consultant psychiatrist where it was proposed that instead of expecting consultants to contact the research team with referrals, the consultant would simply write down the names of suitable clients and leave a list of these with their secretaries. Then, at intervals of approximately a month, a member of the research team would ring each consultant’s secretary to collect details of potential new recruits. This method generally worked although some consultants simply kept forgetting to give the names of suitable patients to their secretaries and as a consequence the study did not recruit any patients from some practices. One consultant psychiatrist suggested that a member of the research team collect the floppy disk containing clinic letters from his secretary once a month in order to obtain details of potential recruits. This method involved the researcher reading all clinic letters and identifying potential recruits.
through the information contained in the letter. Generally, this was a very successful way of finding potential recruits. However, it was often the case that the clinic letters did not contain all the necessary information that the research team needed, such as patient diagnosis, and in these circumstances further details of potential recruits had to be obtained from either the key worker or the consultant psychiatrist. Once the names of potential recruits had been obtained using one of the methods described above, a member of the research team contacted the patients' named key worker in order to confirm details of the patient and their medication change, and to ask their opinion as to the suitability of the patient for the study. It was felt important to speak to the key worker prior to contacting patients because the key worker could provide additional background information about the patient to enable a research team to assess their suitability for the study. For example, in some cases patients did fit all the selection criteria, but were not suitable to be approached because they were extremely suspicious of strangers, and receiving contact from a member of the research team may have exacerbated their psychotic symptoms. In addition, key workers were sometimes able to inform us of the medical history of the patient which had a bearing on their suitability for the study, for example, if the patient had had a head injury, or if there was a doubt over a patients' diagnosis of schizophrenia.

Once the key worker was happy for the patient to be approached directly for study participation, contact with a patient was made in one of two ways; patients living independently in the community were written to with a request for participation, and patients in a residential home or psychiatric unit were approached with details of the study through their key worker or named worker. Once the patient agreed to participate in the study, a member of the research team visited them to answer any remaining questions and to get written consent for study participation. If everything was in order at this stage then testing would begin.
ii) Patient and control testing

Assessments were conducted between June 1998 and July 2002. For patients, assessments of cognitive function and symptom ratings were performed at the place where the patient was currently resident. This was either a psychiatric unit, a care home, or the patient’s private address. Most control assessments were conducted at the subject’s home. A table with chairs within a large room with a plug socket for the CANTAB was the ideal experimental setting for each testing session. Assessments were carried out by the investigator, Philip Tyson, who had previously undergone a period of training with each of the experimental materials used. As the whole testing session can take up to 2 hours to complete, often the assessment was split into 2 sessions of up to one hour each. However, sometimes subjects did not feel fatigued by the tests and were able to complete the assessment in one time period. The order of presentation of the test materials was varied between subjects and between assessments with the same subject so that no patient was presented with the test battery in the same order more than once. The CANTAB tests were run on a Datalux Databrick portable computer with a touch sensitive adjustable monitor (6.5" x 8.5"). To perform the CANTAB tests subjects were seated at a comfortable distance in front of the computer screen so that they could perform each test without having to adjust their seated position. Prior to the CANTAB testing session patients were given practice using the touch screen in the motor screening task.

2.5 Data processing and analysis

The software package SPSS version 9 was used for data analysis. For total symptom ratings on the BPRS and HDS mean scores were used. In addition, on the BPRS mean scores were taken for each of the four symptom dimensions identified by Overall et al. (1976); thought disorder, withdrawal / retardation, hostility / suspiciousness and anxiety / depression. For the cognitive data mean scores were also used for analysis.
All cognitive data sets were examined for normal distributions and the presence of outliers, and group comparisons on these measures were made both with and without outliers present. In the majority of cases this made no difference to the statistical outcome but for sake of consistency all results are presented with outliers excluded.

Independent samples t-tests were used to compare the mean scores between groups at particular time points on demographic, clinical and cognitive variables as appropriate (dropouts vs. continuers; controls vs. patients; patients on typicals vs. patients on atypicals; patients on high 5-HT2A affinity antipsychotics vs. those on low 5HT-2A affinity antipsychotics; patients on multi receptor blocking antipsychotics vs. those on preferential dopamine blocking antipsychotics; patients on fast D2 dissociating antipsychotics vs. those on slower D2 dissociating antipsychotics). For comparisons between the 5 individual medication groups one way analysis of variance was used. If groups differed at baseline on a cognitive variable then comparisons at 9-month and 18-month-follow-up were made with a univariate analysis of variance using baseline scores as a covariate.

To compare changes in performance over the study period, baseline scores were deducted from follow up scores to give a ‘change’ score per variable. An independent samples t-test was then used to compare changes between groups. This procedure was conducted to investigate group differences in changes between baseline and 9-month-follow-up, and between baseline and 18-month-follow-up. Pearson’s R correlations were used to explore associations between cognition, symptoms and demographic variables, and to explore associations between changes in cognition and symptoms.

To control for type 1 errors given the number of statistical tests, it was felt appropriate to use the Bonferroni correction for multiple testing. However, rather than multiply the P value by the total number of tests used, which would increase the chance of a type 2 error, it was considered appropriate to multiply the P value by the number of performance indices which
assessed a particular domain of function. For example, there are 6 symptom ratings in the current study, therefore any significant P value amongst these ratings needs to be multiplied by 6. For the cognitive data, for example, 4 aspects of performance are assessed on the ID/ED test and therefore any P value should be multiplied by 4. The adjusted P value is then compared to the critical value 0.05. The consideration of the impact of the Bonferroni correction on the results is included in the discussion sections, but all P values presented in the results are presented without the Bonferroni correction.

It is recognised that the samples used in the current study are small, and therefore any conclusions drawn from the statistical analysis are tentative.
Chapter 3. Results at baseline

3.1 Missing data

For the demographic data it was not always possible to get a reliable indication of the time of onset of the illness, or of the length of time someone had spent in full time education, and therefore some of this data was missing. In terms of estimates of premorbid I.Q., NART scores were obtained for the majority of cases but two patients had dyslexia and therefore could not be assessed with this measure. Also, three patients refused this particular test. In these circumstances, estimates of premorbid I.Q. were obtained from the score on the Graded Naming Test (GNT) where this score was available. A moderate\(^{11}\) significant positive correlation between NART estimates of premorbid I.Q. and scores on the GNT (\(r=.47; n=67; p < .0005\)) was found in the current study (and was reported in the standardisation study). This indicates that the Graded Naming Test could be used reliably to assess premorbid I.Q. in cases where the NART is not used.

Clinical data was missing for one of two reasons; either the patient refused to answer any questions relating to their illness, this happened in three cases; or there were doubts about the truthfulness of some patient's responses when being interviewed with either the BPRS or the HDS. This happened in one case.

Cognitive data was missing for patients on some tests for a number of reasons. In some circumstances patients simply got tired of the assessment and refused to complete all the tests. In addition, some patients were functioning so poorly on a cognitive level that they did not grasp the instructions to a test and as a consequence did not attempt the test properly. For example, in the Stockings of Cambridge test from the CANTAB battery the patient may have

\(^{11}\) In line with Schimmack & Diener (1997) correlations are considered low if their coefficient value is below .30, moderate if this value is between .30 and .60, and high if this value is above .60.
randomly moved the balls around with no attempt to match the target pattern. On other occasions an active psychosis may have hindered the patients ability to attempt a test reliably, and in these circumstances the test was aborted. For example, one patient was distracted by voices during the presentation stage of the pattern recognition test.

3.2 Demographic data

Patients

In total, 71 patients were recruited for this study although one patient was excluded due to low score on the MMS (21). The remaining 70 patients comprised 44 males (63%) and 26 females (37%). The mean age of the patients was 33, with an age range between 18 and 58. Estimates of years of education were taken using the method described by Crawford & Allan (1997), with 1 year credited for every year spent in full time education, and 0.5 of a year for every year spent in part time education. On average the schizophrenic sample had spent 12 years in full time education, with a range between 9 and 19 years. The mean premorbid I.Q. of this group was 98, ranging between 69 and 121.

Controls

Nineteen control subjects were included in the current investigation and of these 11 were male (58%) and 8 were female (42%). The mean age of the controls was 39, with a range between 18 and 60. On average, the healthy controls had spent 12 years in full time education with a range between 10 and 18 years. The mean premorbid I.Q., for this group was 105 with a range between 84 and 123.
Comparison of patients and controls on demographic variables

Independent samples t-tests did not reveal any significant differences between the patients and controls on demographic variables at the .05 level of statistical significance. However, probability levels approaching significance were observed in terms of premorbid I.Q. and age, with the controls having higher mean values for both variables. A summary of the demographic comparison between patients and controls is presented in Table 3.1.

Table 3.1: Baseline comparisons show marginal evidence of lower age and lower IQ’s for the patient group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (N)</th>
<th>Descriptive statistics</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>sd</td>
</tr>
<tr>
<td>Age</td>
<td>Patients (70)</td>
<td>34</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>39</td>
<td>10.6</td>
</tr>
<tr>
<td>Years of Education</td>
<td>Patients (62)</td>
<td>12</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>12</td>
<td>1.9</td>
</tr>
<tr>
<td>Pre-morbid IQ</td>
<td>Patients (69)</td>
<td>98</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>105</td>
<td>10.5</td>
</tr>
</tbody>
</table>

3.3 Clinical status of the patient sample

At the time of their inclusion in the study the patients had, on average, been ill for 9 years 6 months, with a range between 3 weeks and 38 years. The mean score on the global measure of psychopathology, the BPRS, was 16 although there was considerable variance in symptom presence, with patients scoring between 0 and 35. Similarly, when the BPRS score was broken down according to the four symptom dimensions identified by Overall et al. (1967), there was also considerable variance in the ratings. Ratings of the severity of depression also varied in this patient group, with scores ranging between 1 and 27, with a mean of 10. A summary of the clinical features of the patient sample can be seen in Table 3.2.
### Table 3.2 Summary of the clinical features of the patient sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=</th>
<th>Mean</th>
<th>sd</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of illness</td>
<td>64</td>
<td>9 years 6 months</td>
<td>10 years</td>
<td>3 weeks - 38 years</td>
</tr>
<tr>
<td>BPRS total score</td>
<td>66</td>
<td>16.4</td>
<td>8.5</td>
<td>0 – 35</td>
</tr>
<tr>
<td>BPRS Thinking Disorder</td>
<td>66</td>
<td>6.3</td>
<td>4.4</td>
<td>0 – 21</td>
</tr>
<tr>
<td>BPRS Withdrawal – Retardation</td>
<td>66</td>
<td>3.3</td>
<td>3.8</td>
<td>0 – 16</td>
</tr>
<tr>
<td>BPRS Anxiety - Depression</td>
<td>66</td>
<td>7</td>
<td>3.6</td>
<td>0 – 15</td>
</tr>
<tr>
<td>BPRS Hostile - Suspiciousness</td>
<td>66</td>
<td>2.7</td>
<td>2.6</td>
<td>0 – 12</td>
</tr>
<tr>
<td>HDR score</td>
<td>69</td>
<td>10</td>
<td>6.2</td>
<td>1 – 27</td>
</tr>
</tbody>
</table>

Inter-correlations between clinical features, and between clinical features and demographic variables for the patient group

High positive correlations were found between the BPRS total score and each of the four symptom dimensions, which in turn showed moderate to high positive correlations with each other. These patients therefore, were mildly ill with no particular symptom groups standing out. In addition, both the BPRS total score and its sub-dimensions showed moderate to high positive correlations with the HDS. However, no significant correlations were evident between duration of illness and the BPRS or HDS.

For the demographic variables, age displayed a high positive correlation with duration of illness but no other correlations were found between the clinical and demographic variables.

A summary of these inter-correlations is displayed in Table 3.3.
Table 3.3 Associations between symptom measures; and between demographic variables and clinical variables. (N is between 60 & 71 for all values)

Key: Statistically significant correlations are displayed in shaded boxes\textsuperscript{12}. The key for the BPRS symptom dimensions is as follows; Td = Thought disorder, W / R = Withdrawal / Retardation, A / D = Anxiety /Depression, H / S = Hostility / Suspicion.

<table>
<thead>
<tr>
<th>Cells contain $r (p\text{ value})$</th>
<th>Pre - I.Q.</th>
<th>Education years</th>
<th>Illness duration</th>
<th>BPRS total</th>
<th>BPRS Td</th>
<th>BPRS W / R</th>
<th>BPRS A / D</th>
<th>BPRS H / S</th>
<th>HDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.11 (.34)</td>
<td>.002 (.98)</td>
<td>.73 (&lt;.0005)</td>
<td>.19 (.12)</td>
<td>.16 (.18)</td>
<td>.15 (.20)</td>
<td>.16 (.19)</td>
<td>- .08 (.51)</td>
<td>.23 (.056)</td>
</tr>
<tr>
<td>Premorbid I.Q.</td>
<td>.37 (.003)</td>
<td>.05 (.68)</td>
<td>.14 (.24)</td>
<td>.23 (.055)</td>
<td>- .18 (.13)</td>
<td>.12 (.30)</td>
<td>.18 (.13)</td>
<td>- .02 (.83)</td>
<td></td>
</tr>
<tr>
<td>Education years</td>
<td>- .03 (.81)</td>
<td>- .14 (.28)</td>
<td>- .04 (.73)</td>
<td>- .24 (.059)</td>
<td>- .14 (.27)</td>
<td>- .02 (.82)</td>
<td>- .21 (.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness duration</td>
<td>.21 (.09)</td>
<td>.19 (.13)</td>
<td>.12 (.34)</td>
<td>.10 (.42)</td>
<td>- .03 (.81)</td>
<td>.16 (.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS total</td>
<td></td>
<td></td>
<td></td>
<td>.84 (&lt;.0005)</td>
<td>.69 (&lt;.0005)</td>
<td>.69 (&lt;.0005)</td>
<td>.72 (&lt;.0005)</td>
<td>.60 (&lt;.0005)</td>
<td></td>
</tr>
<tr>
<td>BPRS Td</td>
<td></td>
<td></td>
<td></td>
<td>.46 (&lt;.0005)</td>
<td>.38 (.001)</td>
<td>.71 (&lt;.0005)</td>
<td>.36 (.003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS W / R</td>
<td></td>
<td></td>
<td></td>
<td>.31 (.01)</td>
<td>.46 (&lt;.0005)</td>
<td>.32 (.008)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS A / D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.33 (.006)</td>
<td>.77 (&lt;.0005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS H / S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.36 (.003)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Antipsychotic medication prescribed at baseline

There were different numbers of patients within each medication group because patients were recruited through opportunity sampling and the researchers had no influence on the prescribing practice of the consultant psychiatrists. Similarly, the doses of the medications prescribed differed as a reflection of the clinical need of the patient, although all dosages were within the recommended range according to the BNF. A summary of the antipsychotic medication prescribed at baseline is shown in Table 3.4.

\textsuperscript{12} This is the format that will be used for all correlation matrices in this dissertation.
Table 3.4 Antipsychotic medication prescribed at baseline

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>N</th>
<th>Dose range</th>
<th>Gender split</th>
</tr>
</thead>
<tbody>
<tr>
<td>risperidone</td>
<td>15</td>
<td>2 – 6 mg</td>
<td>11 males 4 females</td>
</tr>
<tr>
<td>olanzapine</td>
<td>16</td>
<td>5 – 20 mg</td>
<td>12 males 4 females</td>
</tr>
<tr>
<td>clozapine</td>
<td>12</td>
<td>25 – 450 mg</td>
<td>9 males 3 females</td>
</tr>
<tr>
<td>quetiapine</td>
<td>11</td>
<td>200 – 500 mg</td>
<td>5 males 6 females</td>
</tr>
<tr>
<td>amisulpride</td>
<td>7</td>
<td>200 – 800 mg</td>
<td>4 males 3 females</td>
</tr>
<tr>
<td>typical(^{\dagger})</td>
<td>9</td>
<td>within routine range</td>
<td>2 males 7 females</td>
</tr>
</tbody>
</table>

3.4 Results from the cognitive tests

The structure of this section will be as follows. Firstly, the mean scores for the patient group will be presented and compared to either normative data or control performance as appropriate. Secondly, associations between test performance and demographic variables for both patients and controls will be presented. For patients, associations between test performance and symptom ratings will also be included.

i) Performance on the Digit span, Graded Naming Test (GNT) and Rivermead Behavioural Memory Test (RBMT)

The mean digit span of the patient group was 6, with a range between 4 and 8. Performance on the GNT was varied, with patients getting between 8 and 27 out of the 30 points available. For the RBMT the mean score was 15 with a range between 4 and 24. A summary of the scores for these tests is shown in Table 3.5.

\(^{\dagger}\) Patients on typical antipsychotics were as follows; 3 on depixol, 3 on thioridazine, and 1 each on haloperidol, chlorpromazine and sulpiride. All doses were within the usual range for each medication according to the BNF.
Table 3.5 Summary of scores on the digit span, Graded Naming and Rivermead

Behavioural Memory Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>Mean score</th>
<th>Range</th>
<th>sd</th>
<th>Performance level (compared to norms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit Span</td>
<td>64</td>
<td>6.0</td>
<td>4 - 8</td>
<td>0.8</td>
<td>Average</td>
</tr>
<tr>
<td>Graded Naming Test</td>
<td>65</td>
<td>17 / 30</td>
<td>8 - 27</td>
<td>4.5</td>
<td>Average</td>
</tr>
<tr>
<td>Rivermead Behavioural Memory test</td>
<td>62</td>
<td>15 / 24</td>
<td>4 - 24</td>
<td>5.3</td>
<td>Moderately impaired</td>
</tr>
</tbody>
</table>

Correlations between scores on the digit span, GNT and RBMT with demographic variables.

Age and years of education both correlated with scores on the RBMT, the former showing a moderate negative correlation whereas the latter showing a low positive correlation. As mentioned previously, the GNT displayed a moderate positive correlation with premorbid I.Q. but with no other clinical or demographic variables. The digit span test did not correlate with any demographic variables. Table 3.6 below displays these correlations.

Table 3.6. Associations between performance on the RBMT and age and years of education and between performance on the GNT and premorbid I.Q. (N is between 54 & 64 for all values)

<table>
<thead>
<tr>
<th>Cells contain r (p value)</th>
<th>Age</th>
<th>Premorbid I.Q</th>
<th>Education Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span</td>
<td>-.07 (.55)</td>
<td>.16 (.20)</td>
<td>.12 (.34)</td>
</tr>
<tr>
<td>GNT</td>
<td>.21 (.08)</td>
<td>.50 (&lt;.0005)</td>
<td>.21 (.10)</td>
</tr>
<tr>
<td>RBMT</td>
<td>-.49 (&lt;.0005)</td>
<td>.21 (.09)</td>
<td>.27 (.04)</td>
</tr>
</tbody>
</table>

Correlations between scores on the digit span, GNT and RBMT with clinical variables

The RBMT displayed low to moderate negative correlations with illness duration, HDS, BPRS total score and all the BPRS dimensions except ‘Hostility / Suspiciousness’. For the digit span and GNT, both displayed low negative correlations with the BPRS dimension.
‘Withdrawal / Retardation’, but with no other clinical variables. These correlations are displayed in Table 3.7.

Table 3.7 Performance on the RBMT was negatively associated with most clinical measures, and digit span and GNT were negatively associated with the BPRS dimension ‘Withdrawal / Retardation’ (N is between 61 & 66 for all values).

<table>
<thead>
<tr>
<th>Cells contain r (p value)</th>
<th>Illness duration</th>
<th>BPRS total</th>
<th>BPRS Td</th>
<th>BPRS W/R</th>
<th>BPRS A/D</th>
<th>BPRS H/S</th>
<th>HDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span</td>
<td>.11 (.41)</td>
<td>-.09 (.48)</td>
<td>.04 (.70)</td>
<td>-.28 (.02)</td>
<td>-.06 (.60)</td>
<td>.21 (.09)</td>
<td>-.06 (.60)</td>
</tr>
<tr>
<td>GNT</td>
<td>-.016 (.90)</td>
<td>-.09 (.47)</td>
<td>.08 (.52)</td>
<td>-.31 (.01)</td>
<td>-.01 (.92)</td>
<td>.07 (.54)</td>
<td>.01 (.89)</td>
</tr>
<tr>
<td>RBMT</td>
<td>-.46 (&lt;.0005)14</td>
<td>-.43 (.001)</td>
<td>-.33 (.009)</td>
<td>-.56 (&lt;.0005)</td>
<td>-.29 (.02)</td>
<td>-.06 (.64)</td>
<td>-.28 (.02)</td>
</tr>
</tbody>
</table>

Summary of baseline results for the digit span, GNT and RBMT.

In terms of the group mean, the patient sample performed within the normal range on the digit span test and GNT. However, their performance on the RBMT was below that expected of healthy controls. For demographic variables, the RBMT was negatively correlated with age, and positively correlated with years of education. In addition, premorbid I.Q. was positively correlated with the GNT. No other associations between tests and demographic variables were evident. For the clinical variables, the RBMT was negatively associated with all measures except the BPRS dimension ‘Hostility / Suspiciousness’. Performance on the digit span and GNT was negatively associated with the BPRS dimension ‘Withdrawal / Retardation’, but with no other clinical variables.

14 This figure was reduced to non significance when the effects of age were taken into account (r=-.17, n=54, p=.20).
ii) Performance on the CANTAB tests

a) Visual Memory Battery

A comparison of performance between the patient group and the control group on the pattern recognition and spatial recognition test

Independent samples t-tests revealed that the patient group performed significantly worse than the control group on both the pattern recognition test and the spatial recognition test. A summary of the scores for each group on the visual memory battery, together with the t-test results can be seen in Table 3.8.

Table 3.8 Comparisons of scores on the visual memory tests show the superior performance of the control group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (N)</th>
<th>Descriptive statistics</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>sd</td>
</tr>
<tr>
<td>Pattern recognition (%)</td>
<td>Patients (56)</td>
<td>77.3</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>Controls (18)</td>
<td>88.2</td>
<td>8.1</td>
</tr>
<tr>
<td>Spatial recognition (%)</td>
<td>Patients (59)</td>
<td>69.6</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>83.1</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Interestingly, paired samples t-tests showed that the patients were significantly worse on the spatial recognition test than on the pattern recognition test ($t=2.89$, with 58 df, $p=.005$). This dissociation was not present in the control sample ($t=1.35$, with 18 df, $p=.19$). However, it could be argued that the disproportionate impairment shown by the patient group on the spatial recognition test relative to the pattern recognition test was merely a feature of task
difficulty, rather than evidence of a dissociation between visual recognition for patterns and locations, with patients simply performing worse on the harder task.\textsuperscript{15}

To investigate this possibility, patients who scored below 75\% on the pattern recognition test were excluded from a second analysis so that patients (n=27) and controls were well matched on the pattern recognition test ($t=-1.74$, with 40 df, $p=.08$) and all patients were scoring within the normal range on this test. A paired samples t-test was then conducted on the remaining patient sample to see if there was still evidence of a disproportionate impairment in spatial recognition. This was still found to be the case ($t=5.46$, with 25 df, $p<.0005$) which shows that even the patients with intact pattern recognition abilities still have an impairment in spatial recognition.

Correlations between performance on the visual memory tests and demographic variables.

A significant moderate negative correlation was observed between the age of the patients and their scores on the pattern recognition test. In addition, a non significant association was observed between age and performance on the spatial recognition test. Neither of these findings were observed in the control sample, either statistically, or by observation of the respective scatterplots. A significant small positive correlation was observed between years of education and spatial recognition score for the patient group but not for the controls. A non significant trend was also observed between years of education and pattern recognition score for this group which was not observed for the controls. Premorbid I.Q. did not correlate with either test of visual memory for the patients or controls. A summary of these scores is shown in Table 3.9.

\textsuperscript{15} The spatial recognition test is a harder task than the pattern recognition test as normal controls typically perform about 6\% better on the former task than on the latter.
Table 3.9 For the patient group age was negatively associated with performance on the pattern recognition test, and years of education was positively associated with performance on the spatial recognition test. \((N\) is between 54 & 59 for all values) 

<table>
<thead>
<tr>
<th>Cells contain (r) (p value)</th>
<th>Age (N)</th>
<th>Premorbid I.Q. (N)</th>
<th>Education Years (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls (19)</td>
<td>Schiz (59)</td>
<td>Controls (19)</td>
</tr>
<tr>
<td>Pattern recognition</td>
<td>- .05 (.83)</td>
<td>- .38 (.003)</td>
<td>.40 (.08)</td>
</tr>
<tr>
<td>Spatial recognition</td>
<td>- .25 (.28)</td>
<td>- .24 (.06)</td>
<td>.26 (.27)</td>
</tr>
</tbody>
</table>

Correlations between performance on the visual memory tests and clinical variables.

Statistically significant negative correlations were found between the pattern recognition test and all clinical measures except duration of illness and the BPRS dimensions ‘Hostility / Suspiciousness’ and ‘Anxiety / Depression’. The \(r\) values for these correlations ranged from low (HDS) to high (Withdrawal / Retardation). For the spatial recognition test, significant negative correlations were observed for 3 out of the 7 symptom measures; BPRS total score, and the sub-dimensions ‘Withdrawal / Retardation’ and ‘Anxiety / Depression’. These \(r\) values were within the low to medium range. These results are summarised in Table 3.10.

Table 3.10 Performance on the visual memory tests were negatively associated some symptom ratings \((N\) is between 57 & 59 for all values),

<table>
<thead>
<tr>
<th>Cells contain (r) (p value)</th>
<th>Illness duration</th>
<th>BPRS total</th>
<th>BPRS Td</th>
<th>BPRS W / R</th>
<th>BPRS A / D</th>
<th>BPRS H / S</th>
<th>HDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern recognition</td>
<td>-.24 (.07)</td>
<td>-.41 (.001)</td>
<td>-.34 (.008)</td>
<td>-.62 (&lt;.0005)</td>
<td>-.23 (.08)</td>
<td>-.09 (.50)</td>
<td>-.29 (.02)</td>
</tr>
<tr>
<td>Spatial recognition</td>
<td>-.14 (.28)</td>
<td>-.33 (.011)</td>
<td>-.23 (.08)</td>
<td>-.47 (&lt;.0005)</td>
<td>-.29 (.02)</td>
<td>-.005 (.97)</td>
<td>-.19 (.14)</td>
</tr>
</tbody>
</table>
Summary of baseline results for the visual memory battery

The patients performed worse than controls on both the pattern recognition and spatial recognition tests. In addition, they were significantly poorer on the spatial recognition test compared with the pattern recognition test. This dissociation between performance on the two tests of visual memory was still present in patients who performed normally on the pattern recognition test. There was no evidence of a comparative dissociation in the control group. A significant positive correlation was observed between patients' performance on the pattern recognition test and the spatial recognition test. This was not found in the control group. In terms of associations between demographic variables and performance on the visual memory tests, negative correlations were observed between the age of the patients and their performance on the pattern recognition test. In addition, a positive correlation was found between years of education and performance on the spatial recognition test. No correlations were observed between demographic variables and performance for the control sample. For the clinical variables, performance on the pattern recognition and spatial recognition tests were negatively associated with several symptom measures.

b) Attentional Battery

A comparison of performance between the patient group and the control group on the ID / ED set shifting test

Independent samples t-tests did not reveal any significant difference between the patients and the controls on the ID / ED test in terms of stage reached, number of errors made at the ED shift, or number of errors made up to the ED shift. However, a significant difference was observed between patients and controls in terms of the total number of errors made on this
test. Here, the patient group made more errors than controls. Table 3.11 summarises these findings.

Table 3.11. Comparisons on the ID/ED test show equitable performance except that the patients made significantly more total errors than controls

<table>
<thead>
<tr>
<th>ID/ED Variable</th>
<th>Group (N)</th>
<th>Descriptive statistics</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>sd</td>
<td>t-value</td>
</tr>
<tr>
<td>Stage reached</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (49)</td>
<td>8.0</td>
<td>1.0</td>
<td>-.72</td>
</tr>
<tr>
<td>Controls (19)</td>
<td>8.2</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Errors at ED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (48)</td>
<td>16.0</td>
<td>10.8</td>
<td>.95</td>
</tr>
<tr>
<td>Controls (19)</td>
<td>13.2</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>Total Errors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (52)</td>
<td>39.0</td>
<td>11.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Controls (19)</td>
<td>20.6</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>Errors up to ED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (44)</td>
<td>7.5</td>
<td>2.7</td>
<td>-.92</td>
</tr>
<tr>
<td>Controls (19)</td>
<td>8.8</td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

Correlations between demographic variables and performance on the ID/ED test.

A positive correlation was observed for the patients between premorbid I.Q. and stage reached on the ID / ED test. This correlation was not observed in the control group. Similarly, premorbid I.Q. and errors at ED shift correlated negatively for the patient group but not for the control group. Neither age nor years of education correlated with any performance indicator on the ID/ED test in either the patients or controls. Table 3.12 summarises these results.

Table 3.12 Premorbid I.Q. was positively associated with stage reached, and negatively associated with errors at ED shift for the patient group on the ID/ED test.

<table>
<thead>
<tr>
<th>Cells contain r (p value)</th>
<th>Age</th>
<th>Premorbid I.Q.</th>
<th>Education Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Schiz (48-N&lt;56)</td>
<td>Controls (N=19)</td>
</tr>
<tr>
<td>Stage reached</td>
<td>-.14 (.29)</td>
<td>-.24 (.31)</td>
<td>.38 (.003)</td>
</tr>
<tr>
<td>Errors at ED shift</td>
<td>-.12 (.38)</td>
<td>.37 (.11)</td>
<td>-.43 (.002)</td>
</tr>
<tr>
<td>Errors up to ED shift</td>
<td>.12 (.40)</td>
<td>.16 (.51)</td>
<td>.17 (.23)</td>
</tr>
<tr>
<td>Total errors</td>
<td>.14 (.29)</td>
<td>.32 (.18)</td>
<td>-.26 (.056)</td>
</tr>
</tbody>
</table>
Correlations between clinical variables and performance on the ID/ED test.

Significant negative correlations were found between stage reached on the ID/ED test and BPRS total score and the sub-dimensions ‘Thought disorder’ and ‘Withdrawal/Retardation’.

A significant negative correlation was also observed between errors up to ED shift and HDS score. These results are highlighted in Table 3.13 below.

Table 3.13 Stage reached on the ID/ED test was negatively associated with BPRS total and BPRS dimensions ‘Thought Disorder’ and ‘Withdrawal/Retardation’, and errors up to ED shift was negatively associated with HDS score. (N is between 46 & 54 for all values).

<table>
<thead>
<tr>
<th>Cells contain r (p value)</th>
<th>Illness duration</th>
<th>BPRS total</th>
<th>BPRS Td</th>
<th>BPRS W/R</th>
<th>BPRS A/D</th>
<th>BPRS H/S</th>
<th>HDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage reached</td>
<td>-.26 (.057)</td>
<td>-.27 (.04)</td>
<td>-.27 (.04)</td>
<td>-.55 (&lt;.0005)</td>
<td>-.05 (.67)</td>
<td>.11 (.39)</td>
<td>-.10 (.43)</td>
</tr>
<tr>
<td>Errors at ED shift</td>
<td>-.08 (.59)</td>
<td>-.15 (.28)</td>
<td>-.18 (.20)</td>
<td>.12 (.41)</td>
<td>-.15 (.29)</td>
<td>-.18 (.22)</td>
<td>-.03 (.80)</td>
</tr>
<tr>
<td>Errors up to ED shift</td>
<td>.14 (.33)</td>
<td>-.06 (.67)</td>
<td>-.03 (.83)</td>
<td>-.02 (.87)</td>
<td>-.09 (.52)</td>
<td>.09 (.53)</td>
<td>-.33 (.02)</td>
</tr>
<tr>
<td>Total errors</td>
<td>.06 (.64)</td>
<td>.07 (.57)</td>
<td>.07 (.57)</td>
<td>.11 (.39)</td>
<td>.07 (.60)</td>
<td>-.02 (.87)</td>
<td>-.03 (.83)</td>
</tr>
</tbody>
</table>

Summary of baseline results for the attentional battery

The patient group did not differ from the control group on the ID/ED test in terms of stage reached, number of errors made at the ED shift or number of errors made up to the ED shift.

However, they did make significantly more errors overall. A number of inter-correlations were found between different performance indicators for both the patients and controls. In terms of the relationship between demographic variables and performance, a positive correlation was found between premorbid I.Q. and stage reached for the patient group but not the control group. In addition, errors at the ED shift correlated negatively with premorbid I.Q. for the patients but not for the control group. Finally, in terms of the association between symptoms and performance on the ID/ED test, BPRS total score and the sub-dimensions...
Thought disorder and Withdrawal / Retardation showed negative correlations with stage reached on the ID/ED test, and a negative correlation was observed between HDS score and errors up to ED shift.

c) Working memory battery

A comparison of performance between the patient group and the control group on the working memory battery.

The patient group performed significantly worse on the spatial span test than the control group and could on average, remember one item fewer than the controls. Similarly, independent-samples t-tests revealed that the patient group performed significantly worse on the spatial working memory test than the controls both in terms of strategy score and between-search errors. Table 3.14 shows these results.

Table 3.14 The patient group performed at a lower level than controls on tests of working memory.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (N)</th>
<th>Descriptive statistics</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>sd</td>
</tr>
<tr>
<td>Spatial span</td>
<td>Patients (50)</td>
<td>4.3</td>
<td>.85</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>5.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Spatial span</td>
<td>Patients (53)</td>
<td>37.5</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>Controls (16)</td>
<td>33.7</td>
<td>2.4</td>
</tr>
<tr>
<td>SPW errors</td>
<td>Patients (57)</td>
<td>45.6</td>
<td>22.1</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>22.6</td>
<td>16.0</td>
</tr>
</tbody>
</table>
Correlations between demographic variables and performance on the working memory battery

For the patient group, age was significantly negatively associated with spatial span performance, and premorbid I.Q. was significantly negatively associated with between-search errors. Both of these associations were moderate in degree. For the controls, the only significant correlation was between age and between search errors. This was a high correlation. Years of education did not correlate with performance on this test for either group. These results are shown in Table 3.15.

Table 3.15 The correlations between demographic variables and performance on the working memory tests for patients and controls.

<table>
<thead>
<tr>
<th>Cells contain r (p value)</th>
<th>Age</th>
<th>Premorbid I.Q.</th>
<th>Education Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial span</td>
<td>-.43 (&lt;.0005)16</td>
<td>-.377 (.11)</td>
<td>.11 (.37)</td>
</tr>
<tr>
<td>SWM Strategy</td>
<td>-.04 (.72)</td>
<td>.29 (.22)</td>
<td>-.25 (.053)</td>
</tr>
<tr>
<td>SWM between search errors</td>
<td>.11 (.40)</td>
<td>.61 (.006)</td>
<td>-.38 (.003)</td>
</tr>
</tbody>
</table>

Correlations between clinical variables and performance on the working memory battery

A significant negative correlation was observed between spatial span and time-since-onset, although this correlation was reduced to non significance when the effect of patient age was partialled out (r=-.0005; p=.997). No correlations were observed between duration of illness and the spatial working memory test, or between any part of the working memory battery or BPRS total score or HDS. However, the ‘Withdrawal / Retardation’ dimension of the BPRS did correlate negatively with spatial span, and positively with between search errors. These results are displayed in Table 3.16.

16 This association remained significant after controlling for the effects of duration of illness (r=-.32, p=.014)
Table 3.16 Shows that the BPRS dimension 'Withdrawal / Retardation' was

negatively associated with spatial span and positively associated with between search

errors (N is between 55 & 60 for all values)

<table>
<thead>
<tr>
<th>Cells contain</th>
<th>r (p value)</th>
<th>Illness duration</th>
<th>BPRS total</th>
<th>BPRS Td</th>
<th>BPRS W / R</th>
<th>BPRS A / D</th>
<th>BPRS H / S</th>
<th>HDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial span</td>
<td>-.29 (.02)17</td>
<td>-.12 (.32)</td>
<td>-.02 (.87)</td>
<td>-.39 (.002)</td>
<td>-.04 (.75)</td>
<td>.16 (.20)</td>
<td>.02 (.84)</td>
<td></td>
</tr>
<tr>
<td>SWM strategy</td>
<td>-.18 (.17)</td>
<td>-.05 (.69)</td>
<td>-.10 (.45)</td>
<td>.08 (.55)</td>
<td>-.05 (.68)</td>
<td>-.21 (.11)</td>
<td>-.07 (.57)</td>
<td></td>
</tr>
<tr>
<td>SWM between search errors</td>
<td>.05 (.70)</td>
<td>.17 (.20)</td>
<td>.05 (.71)</td>
<td>.54 (&lt;.0005)</td>
<td>.05 (.67)</td>
<td>-.20 (.13)</td>
<td>.02 (.82)</td>
<td></td>
</tr>
</tbody>
</table>

Summary of baseline results for the working memory battery.

The patient group were significantly impaired on the spatial span test and both performance indices of the spatial working memory test compared to the control group. In terms of the correlations between these tests and demographic variables, for the patient group negative associations were observed between age and spatial span, and between premorbid I.Q. and between-search errors. For the controls the only significant correlation was a positive one between age and between search errors. After controlling for age, duration of illness did not correlate with any working memory measure. For symptom variables, there was a positive association between the BPRS dimension ‘Withdrawal / Retardation’ and spatial span, and a negative association between this dimension and spatial working memory between-search errors. No other correlations were evident between the working memory tests and symptom ratings.

17 This figure was reduced to non significance when the effects of age were partialed out (r=-.0005; p=.997)
d) Planning battery

A comparison of performance between the patient group and the control group on the Stockings of Cambridge Test

The patient group made significantly fewer minimum-move solutions than the control group (6.98 vs. 9.17). For initial thinking times, the patient group were significantly quicker than controls for composite times, as well as for 2 move, 4 move and 5 move problems. These results are displayed in Table 3.17 and Chart 3.1.

*Table 3.17 The patients' problem solving abilities were less efficient than that of the controls, but they were quicker at attempting to solve most of the problems.*

<table>
<thead>
<tr>
<th>Stockings of Cambridge Variable</th>
<th>Group (N)</th>
<th>Descriptive statistics (msec)</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>sd</td>
</tr>
<tr>
<td>Minimum move solutions</td>
<td>Patients (52)</td>
<td>6.98</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Controls (17)</td>
<td>9.17</td>
<td>1.7</td>
</tr>
<tr>
<td>Composite mean initial think times</td>
<td>Patients (49)</td>
<td>4876</td>
<td>2862</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>7066</td>
<td>2536</td>
</tr>
<tr>
<td>Mean initial think times 2 move problems</td>
<td>Patients (49)</td>
<td>1673</td>
<td>1152</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>2446</td>
<td>1212</td>
</tr>
<tr>
<td>Mean initial think times 3 move problems</td>
<td>Patients (50)</td>
<td>5810</td>
<td>4103</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>6002</td>
<td>3062</td>
</tr>
<tr>
<td>Mean initial think times 4 move problems</td>
<td>Patients (48)</td>
<td>4749</td>
<td>3023</td>
</tr>
<tr>
<td></td>
<td>Controls (18)</td>
<td>8000</td>
<td>4061</td>
</tr>
<tr>
<td>Mean initial think times 5 move problems</td>
<td>Patients (49)</td>
<td>5715</td>
<td>4118</td>
</tr>
<tr>
<td></td>
<td>Controls (19)</td>
<td>11140</td>
<td>5361</td>
</tr>
</tbody>
</table>

No significant differences were found between the patients and controls in terms of composite subsequent think times, or for four move or five move problems. However, the patients utilised significantly more subsequent thinking times for 2 move and 3 move problems. These results are shown in table 3.18 and chart 3.2.
Table 3.18 There were no differences in subsequent thinking times between the groups, except that the patients were slower at attempting to solve 3 move problems.

<table>
<thead>
<tr>
<th>Stockings of Cambridge Variable</th>
<th>Group (N)</th>
<th>Descriptive Statistics (msec)</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>sd</td>
</tr>
<tr>
<td>Composite mean subsequent think times</td>
<td>Patients (49)</td>
<td>944</td>
<td>581</td>
</tr>
<tr>
<td></td>
<td>Controls (17)</td>
<td>742</td>
<td>730</td>
</tr>
<tr>
<td>Mean subsequent think times 2 move problems</td>
<td>Patients (48)</td>
<td>287</td>
<td>418</td>
</tr>
<tr>
<td></td>
<td>Controls (17)</td>
<td>79</td>
<td>101</td>
</tr>
<tr>
<td>Mean subsequent think times 3 move problems</td>
<td>Patients (45)</td>
<td>328</td>
<td>469</td>
</tr>
<tr>
<td></td>
<td>Controls (17)</td>
<td>91</td>
<td>138</td>
</tr>
<tr>
<td>Mean subsequent think times 4 move problems</td>
<td>Patients (52)</td>
<td>1596</td>
<td>1223</td>
</tr>
<tr>
<td></td>
<td>Controls (17)</td>
<td>1207</td>
<td>1072</td>
</tr>
<tr>
<td>Mean subsequent think times 5 move problems</td>
<td>Patients (49)</td>
<td>1190</td>
<td>776</td>
</tr>
<tr>
<td></td>
<td>Controls (18)</td>
<td>1490</td>
<td>1828</td>
</tr>
</tbody>
</table>

Chart 3.1 Initial thinking times for the controls on the Stockings of Cambridge test increases monotonically with task difficulty, whereas for the patients initial think time remains constant from 3 move problems onwards.
Chart 3.2 The controls consistently needed less subsequent thinking time than the schizophrenics except for 5 move problems.

Correlations between demographic variables and performance indices on the Stockings of Cambridge test

For the patient group, neither composite initial think times or composite subsequent think times showed any association with demographic variables. However, low positive significant correlations were found between age and both initial and subsequent thinking times at some stages of the task. For the controls, a moderate positive association was present between age and composite subsequent think times but not composite initial think times. In addition, age and premorbid I.Q. also correlated with performance on some of the sub stages of the test. These results are summarised in table 3.19.
Table 3.19 Age was associated with some performance indices on the Stockings of Cambridge test for both patients and controls, and premorbid I.Q. was also associated with performance, but only for the control group.

Correlations between clinical variables and performance indices on the Stockings of Cambridge test

Duration of illness was positively associated with initial thinking times for 2 move problems, and composite subsequent think times as well as subsequent think times for 4 and 5 move problems. These associations were all moderate in degree. However, after the effects of the patient’s age was partialled out the only significant correlations that remained were between duration of illness and composite subsequent think times ($r = .36; n=47; p = .009$) and between duration of illness and subsequent think times for 4 move problems ($r = .29; n=47; p = .037$), although the association between duration of illness and initial think time for 2 move problems remained close to significance ($r = .262; n=47; p = .069$). In addition, the BPRS dimensions ‘Thought disorder’ and ‘Hostility / Suspiciousness’ were negatively associated with subsequent think time for 5 move problems. No other associations were found between clinical variables and performance on the Stockings of Cambridge test. These results are summarised in Table 3.20.
Table 3.20 Illness duration was positively associated with thinking times at certain stages of the test, and the BPRS dimensions of 'Thought Disorder' and 'Hostility/Suspiciousness' were positively associated with subsequent thinking times at the 5 move problem stage (N is between 50 & 55 for all values).

<table>
<thead>
<tr>
<th>Cells contain</th>
<th>Illness Duration</th>
<th>BPRS total</th>
<th>BPRS Td</th>
<th>BPRS W/R</th>
<th>BPRS A/D</th>
<th>BPRS H/S</th>
<th>HDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Move Solutions</td>
<td>-0.04 (.76)</td>
<td>0.04 (.75)</td>
<td>-0.02 (.88)</td>
<td>-0.11 (.42)</td>
<td>0.09 (.51)</td>
<td>0.11 (.43)</td>
<td>0.16 (.24)</td>
</tr>
<tr>
<td>ITT Composite</td>
<td>0.17 (.22)</td>
<td>-0.06 (.65)</td>
<td>-0.08 (.56)</td>
<td>-0.10 (.45)</td>
<td>0.09 (.94)</td>
<td>0.08 (.56)</td>
<td>0.12 (.38)</td>
</tr>
<tr>
<td>ITT-2 move problems</td>
<td>0.40 (.003)</td>
<td>-0.07 (.59)</td>
<td>-0.04 (.75)</td>
<td>0.02 (.85)</td>
<td>0.08 (.55)</td>
<td>-0.15 (.29)</td>
<td>0.1 (.36)</td>
</tr>
<tr>
<td>ITT-3 move problems</td>
<td>-0.001 (.99)</td>
<td>-0.20 (.14)</td>
<td>-0.16 (.24)</td>
<td>-0.14 (.30)</td>
<td>-0.11 (.41)</td>
<td>0.20 (.14)</td>
<td>0.03 (.83)</td>
</tr>
<tr>
<td>ITT-4 move problems</td>
<td>0.19 (.17)</td>
<td>0.13 (.35)</td>
<td>0.09 (.52)</td>
<td>-0.12 (.39)</td>
<td>0.18 (.19)</td>
<td>0.05 (.68)</td>
<td>0.22 (.11)</td>
</tr>
<tr>
<td>ITT-5 move problems</td>
<td>0.12 (.38)</td>
<td>-0.23 (.10)</td>
<td>-0.26 (.06)</td>
<td>-0.23 (.10)</td>
<td>-0.16 (.24)</td>
<td>-0.18 (.20)</td>
<td>-0.05 (.70)</td>
</tr>
<tr>
<td>STT Composite</td>
<td>0.43 (.002)</td>
<td>-0.08 (.55)</td>
<td>-0.11 (.43)</td>
<td>0.19 (.17)</td>
<td>0.06 (.63)</td>
<td>-0.20 (.14)</td>
<td>-0.017 (.90)</td>
</tr>
<tr>
<td>STT-2 move problems</td>
<td>0.25 (.07)</td>
<td>0.18 (.19)</td>
<td>0.17 (.21)</td>
<td>0.27 (.051)</td>
<td>0.03 (.80)</td>
<td>0.16 (.24)</td>
<td>-0.05 (.72)</td>
</tr>
<tr>
<td>STT-3 move problems</td>
<td>0.18 (.19)</td>
<td>-0.04 (.74)</td>
<td>-0.04 (.77)</td>
<td>0.09 (.52)</td>
<td>0.06 (.63)</td>
<td>-0.09 (.52)</td>
<td>0.09 (.49)</td>
</tr>
<tr>
<td>STT-4 move problems</td>
<td>0.40 (.003)</td>
<td>-0.11 (.42)</td>
<td>-0.13 (.36)</td>
<td>0.22 (.10)</td>
<td>0.16 (.25)</td>
<td>-0.24 (.08)</td>
<td>-0.03 (.80)</td>
</tr>
<tr>
<td>STT-5 move problems</td>
<td>0.35 (.01)</td>
<td>-0.21 (.14)</td>
<td>-0.29 (.04)</td>
<td>0.01 (.91)</td>
<td>0.18 (.20)</td>
<td>-0.34 (.01)</td>
<td>-0.03 (.78)</td>
</tr>
</tbody>
</table>

Summary of baseline results for the planning battery

The patient group performed significantly poorer on the Stockings of Cambridge test than the controls in terms of the number of solutions that were found within the minimum number of moves. For initial thinking time, the patient group were significantly faster than the controls at most stages of the test. The opposite pattern was observed for subsequent think times at the 2 and 3 move problem stage. Here the patients utilised significantly more thinking time than controls. Many inter-correlations were observed between different performance indices on the Stockings of Cambridge test for both patients and controls. In terms of demographic variables, there was a tendency for age to be associated with performance for both groups, and for the controls in particular premorbid I.Q. was negatively associated with subsequent think times. For clinical variables, duration of illness was associated with some aspects of performance, but few other associations were observed.

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This figure was reduced to non significance when the effects of the patient's age was partialled out (r=.19; n=47; p=.18).
Chapter 4. Discussion of baseline results

Baseline results will be discussed in terms of the distinct aspects of cognition that the tests measured; namely — short term memory, working memory, long term memory, semantic memory, attention and planning. In addition, consideration will be given to the associations between cognitive performance and demographic and clinical variables.

4.1 Short-term memory

Digit span

This task is a measure of verbal short term memory capacity and involves the ability to hold verbal information 'on line'. The mean digit span of the patient sample was 6, with a standard deviation of 0.8. This level of performance is similar to other studies that have investigated short term verbal memory in schizophrenia where mean spans of 5.7, 5.8, 5.8, 5.9 and 6 have been reported respectively (Stirling et al. 1997; Conklin et al. 2000, Gruzelier et al. 1988, Fossati et al. 1999, Beatty et al. 1993). In these studies the digit spans reported for the patient samples were significantly lower than those reported for matched controls, whose mean spans ranged between 6.8 (Stirling et al. 1997) to 8.9 (Beatty et al. 1993), suggesting that short term verbal memory is impaired in schizophrenia. Indeed, this finding has been reported in other studies (Perry et al. 2001; Goldberg et al. 1998; Weiss et al. 1988), and a recent meta-analysis came to the same conclusion (Aleman et al. 1999).

However, several studies have not found that patients exhibit a deficit on the digit span test (Kolb & Whishaw, 1983; McKenna et al., 1990; Park & Holzman, 1992; Tamlyn et al. 1992; Goldberg et al. 1993; Duffy and O'Carroll, 1994; Morice & Delahunty, 1996; Kenny & Meltzer, 1991). An explanation for this conflicting evidence has been offered by Stirling et
al. (1997) who point out methodological limitations with the studies that found no impairment on the digit span task. For example, neither Tamlyn et al. (1992) nor Duffy & O'Carroll (1994) used a control group in their studies and comparisons with existing normative data may be unreliable because performance might be influenced by a number of extraneous variables that differ between studies (e.g., clarity of speech or rate of digit delivery). In addition, McKenna et al. (1990) used the digit span test from the Middlesex Elderly Assessment of Mental State in their study. This test has a maximum value of 5 and it is therefore likely that ceiling effects may have masked superior performance by controls. Finally, Park & Holzman (1992) employed a sample size of just 12 cases which is arguably an insufficient number of subjects from which to draw general conclusions. Stirling et al (1997) conclude that the majority of studies of digit span performance in schizophrenia that have used a control group have found an impairment.

On a cognitive level, it has been proposed that digit span performance is dependent on the ability of a subject to maintain information in short term memory through subvocal articulatory rehearsal (Baddeley, 1986). There are limits to the amount of information that can be held in this system (Miller, 1956), and on this basis it has been suggested that patients with schizophrenia have less storage capacity than controls (Goldberg et al. 1998). An alternative explanations for the digit span deficit suggests that there are problems with the appropriate allocation of attentional resources to the task (Goldberg et al. 1998). Here, the patient is susceptible to distraction from external or internal sources and therefore can not focus efficiently when the digits are presented. Goldberg et al. (1998) sought to investigate which of these possible explanations was the more feasible one using a number of digit span trials with varying memory load. If an attentional impairment was the cause of the deficit then digit span performance would be disrupted irrespective of the number of digits to be remembered. However, if the storage capacity hypothesis is correct then the patients would be more impaired the larger the number of digits to be remembered. The study found that the patients had more difficulty remembering larger number strings suggesting that the misallocation of
attentional resources is not the explanation for this deficit. In addition, Goldberg et al (1998) found that in a word remembering task performance was disproportionately impaired (compared to controls) when distractors were present which prevented rehearsal, when there was longer delays between presentation and recall, and when the set sizes were larger. These results confirm that patients with schizophrenia have a reduced ability to maintain verbal material in the short term memory store. On the whole the evidence from the present investigation and from previous research suggests that patients with schizophrenia have an impairment in verbal short term memory which is due to capacity limitations rather than a misallocation of attentional resources.

Although the brain regions responsible for verbal short term memory are still largely unknown, several areas have been implicated. Lesion studies have suggested the involvement of the left parietal region (McFie, 1975; Newcombe, 1969), and MRI studies have implicated the right middle and medial frontal gyri, the right inferior parietal lobule, and the left middle and inferior frontal gyri (Tsukiura et al. 2001).

Associations between demographic variables, clinical variables and performance on the digit span test

Performance on the digit span test was not associated with any demographic variables. However, in terms of clinical variables, performance was negatively correlated with the BPRS dimension ‘withdrawal / retardation’. As this BPRS dimension can be considered to reflect negative symptoms, this finding suggests that negative aspects of schizophrenia do have an influence on verbal short term memory. Previous research that has investigated this issue has yielded inconsistent results. On the one hand, some authors have found an association between negative symptoms and digit span performance (Stirling et al. 1997; Aleman et al. 1999), whereas many other authors have found no association between these variables (Fossati et al. 1999; Addington et al. 1997; Stratta et al. 1997; Brebion et al. 1997; Goldberg 103
As an attempt to explain these conflicting results, perhaps digit span performance is not clearly associated with negative symptoms per se, but with other more subtle symptoms that differ between patients across different studies. Indeed, in support of this idea, Docherty & Gordinier (1999) found that communication disturbances were associated with poor performance on the digit span test.

Spatial span

This task is a measure of spatial short term memory capacity and involves the ability to hold visuo-spatial information ‘on line’. The patient group achieved a mean spatial span of 4.3 with a standard deviation of 0.8. This level of performance was significantly worse than that of the control group (mean = 5.6), who performed at a similar level to the CANTAB norms (mean = 5.5). This result is unaffected by the Bonferroni correction for multiple testing, and indicates that the ability to hold visuo-spatial information on line is compromised in schizophrenia.

Previous studies using the spatial span test from the CANTAB battery have also reported a deficit in comparison with matched controls (Pantelis et al. 1997; Hutton et al. 1998; Elliott et al. 1998), although there was some variability in the mean level of performance between these studies. Pantelis et al. (1997) reported that their schizophrenic patients achieved a mean spatial span of just 3.7, whereas Hutton et al. (1998) and Elliott et al. (1998) reported mean spans of 5.4, and 4.9 respectively. Investigations using the Dot Enumeration Perceptual Organisation Task (Rabinowicz et al. 1996), the visual memory span test from the Wechsler Memory Scale -revised (Wechsler, 1987), and the Corsi block tapping test (Corsi, 1972) have also found that patients with schizophrenia have an impairment in short term visuo-spatial memory (Perry et al. 2001; Salame et al. 1998; Rabinowicz et al. 1996; Fleming et al. 1997;
Kenny & Meltzer, 1991; Gruzelier et al. 1988). However, impairments have not always been reported (Tamlyn et al., 1992; Kolb & Whishaw, 1983).

Perhaps these inconsistent findings are due to methodological differences between studies, such as those that may account for the conflicting findings within short term verbal memory research in schizophrenia. Where deficits have been found, explanations have suggested a problem with the allocation of processing resources for the consolidation of the memory trace in short term visual memory. This impairment occurs after initial perceptual processing has been successfully completed within the sensory store (Rabinowicz, 1996).

Neuropathologically, it has been suggested that the spatial span task is subserved by the middle section of the ventrolateral frontal cortex (Brodmann areas 45 and 47) (Petrides, 1994), and this suggestion has been confirmed in a PET investigation which found that a spatial span task did activate the ventrolateral prefrontal cortex (Brodmann area 47) (Owen et al. 1996).

**Associations between demographic variables, clinical variables and performance on the spatial span test**

In the current study, spatial span correlated negatively with age for the schizophrenic group but neither years of education nor premorbid I.Q. showed any degree of association with this test. The finding of lower visual span scores with increasing age in schizophrenia has been reported previously (Pantelis et al. 1997), although it appears that a decline in short term visual memory with age is a natural process, as this has been demonstrated previously in healthy controls (Boyle et al. 1975). Indeed, the CANTAB norms show an age related decline in spatial span (e.g., for controls aged <35 span = 6.6, 35-49 span = 6, 50-59 span = 5.4).

19 To add to this study, Fossati et al. (1999) reported that their group of schizophrenic patients performed at the same level as that of controls on a spatial span test. However, the difference in
However, spatial span and age did not correlate for the controls in the current study, although this might be explained as being due to small numbers in the control sample.

In terms of clinical variables, there was no correlation between spatial span and any of the clinical variables under investigation. A lack of association between visuo-spatial short term memory and symptoms has been reported earlier (Pantelis et al. 2001; Fossati et al. 1999; Elliot et al. 1998) suggesting that the neural substrates responsible for spatial span performance and those responsible for psychiatric symptoms are distinct. In terms of the lack of association between duration of illness and spatial span, this finding does concur with previous investigations suggesting that short term visual memory does not decline with increasing length of illness (Pantelis et al. 1997; Elliott et al. 1998; Verdoux & Liraud, 2000).

**Associations between digit span and spatial span performance in schizophrenia**

In addition to the finding in the current study of a deficit of both digit span and spatial span in schizophrenia, a significant positive correlation was observed between performance on these measures \((r = .29, n = 59; p = .023)\). Within the working memory model proposed by Baddeley (1981, 1986), this pattern of results would seem to suggest that in schizophrenia there is a deficit at the level of the central executive which limits the processing capability of the modality specific slave systems – those responsible for short term verbal and visual memory. To be consistent with this suggestion, an impairment of the central executive should theoretically also lead to an impairment of the third slave system, the primary acoustic store, which is concerned with non verbal auditory information. Although the current study did not include a measure of this store, recent research has found such a deficit (March, 1999), which does support the current suggestion that the central executive is impaired in schizophrenia. Other investigators have also reported evidence to suggest a central executive impairment in short term memory (Perry et al. 2001).

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\text{performance was almost significant between the two groups (5.8 Vs 6.7, } p = .06)\]
However, Spindler et al. (1997) examined short term memory tasks involving objects and locations, and although schizophrenics were impaired on both tasks, the deficits were no greater when the tasks were combined than when they were presented independently. These findings suggest that it is downstream slave systems which are impaired in schizophrenia rather than the central executive. Clearly much more investigation is needed in this area.

4.2 Working memory

Spatial Working Memory

This test involves two important components of working memory, the ability to maintain information 'on line', and the ability to utilise this information to perform other cognitive operations. Here, the schizophrenic group were impaired relative to controls on both aspects of this test — search strategy and between search errors. Both P values remained highly significant after controlling for multiple testing. A poor strategy score indicates a failure to utilise a search strategy when locating tokens, whereas between search errors reflect a difficulty in keeping track of the boxes that had already contained a token whilst looking for a new token.

Previous studies of schizophrenia using the spatial working memory test from the CANTAB battery have yielded comparable results to the current study. Hutton et al. (1998) found that first episode schizophrenics were impaired in terms of between search errors and strategy score compared to controls. Pantelis et al. (1997) reported similar results with their sample of schizophrenics performing at a significantly lower level than that of controls on both performance indices of the spatial working memory test. Interestingly, this schizophrenic group also performed worse than patients with frontal lobe lesions, temporal lobe / amygdalo-hippo-campal lesions, and Parkinson's disease on this test. In addition, Elliott et al. (1998) found that even schizophrenic patients with preserved intellectual function were still impaired.
in comparison to controls in terms of between search errors on the more difficult levels of the spatial working memory test. These patients also showed a trend towards impaired strategy. Other investigations of spatial working memory using a variety of experimental paradigms have also reported a deficit in schizophrenia (Minor & Park, 1999; Fleming et al., 1997; Spindler et al., 1997; Keefe et al., 1995; Park & Holzman, 1992), although one early investigation did not find an impairment (Kolb & Whishaw, 1983).

Neuropathological explanations of the spatial working memory deficit implicate the involvement of the prefrontal cortex. The evidence comes from a variety of sources; in primate studies lesions of the prefrontal cortex impair spatial working memory (e.g., Jacobson, 1936); humans with frontal lobe damage (through disease or injury) are usually impaired on tasks reliant on working memory abilities (e.g., Moskovitch, 1994a); evidence from PET, fMRI, EEG, neurochemical and post mortem investigations indicate that the prefrontal cortex is abnormal in schizophrenia (e.g., Gur, 2000; Crespo-Facorro, 1999; Ohnuma, 1999).

Taken together, the evidence indicates that the prefrontal cortex is important for tasks involving working memory and that on a neuropathological level this region is abnormal in schizophrenia. This results in impaired performance on working memory tasks in this patient group.

More specifically, Petrides (1994) suggested that performance on spatial working memory tasks is mediated by two executive processing systems located within the lateral frontal cortex. For the active comparison of stimuli held in short term memory and the co-ordination of the appropriate response, the middle portion of the ventrolateral frontal cortex (Brodmann areas 44 and 47) is important. On the other hand, the active manipulation and monitoring of information which is held on line is mediated by the mid-dorsolateral frontal cortex.
(Brodman areas 46 and 9). Owen et al. (1996) investigated this suggestion using PET and the CANTAB tests of spatial span and spatial working memory. As predicted, the spatial span test was shown to activate the ventrolateral prefrontal cortex (area 47), whereas the mid-dorsolateral prefrontal cortex (areas 46 and 9) was activated by the spatial working memory task. These findings indicate that the ventrolateral and dorsolateral are important areas for spatial working memory tasks, and support the notion that these circuits are compromised in schizophrenia.

Associations between demographic variables, clinical variables and performance on the spatial working memory test

In terms of the associations between demographic variables and performance on this test, age correlated positively with between search errors for the controls but not for the schizophrenics. This finding with regard to the control pattern of results is consistent with the CANTAB normative data as the number of between search errors does increase with age. For example, controls aged <35 have a mean between-search error rate of 17.5, whereas controls aged 35-49, 50-59 and 60-69, have mean error rates of 34.4, 45.3 and 52.6 respectively. Perhaps the finding of a lack of correlation between age and between search errors for the schizophrenic group merely confirms that working memory systems are disrupted in this disorder, and therefore do not show the usual age related changes. This finding is also consistent with reports that the spatial working memory deficit is a stable marker for schizophrenia which does not normalise over time (Park et al. 1999), although this suggestion has recently been challenged on an empirical basis (Okada, 2002).

The reverse pattern of results was observed in terms of the association between premorbid I.Q. and between search errors. Here, a negative correlation was observed for the schizophrenic group but not for the controls. This finding of higher premorbid I.Qs to be associated with less errors on the spatial working memory test for schizophrenic patients was
not found in the only other study to investigate such an association (Pantelis et al., 1997). However, our current finding is consistent with wider literature which suggests a link between higher premorbid educational attainment and better cognitive function in general (Swanson et al., 1998). However, in the current study years of education was not associated with between search errors in either the schizophrenic sample nor the control sample. One possible explanation for this discrepancy may be that although there is a wide variability in the premorbid I.Q. of the schizophrenic patients, in terms of years of education the range is very limited (i.e., 68.8% of patients had been in education for between 9 and 12 years). This restricted range may be one reason why no association was found. Another explanation may be that the relationship between years of education and between search errors may be non-linear. In addition, it should be noted that years of education might not provide a very accurate indication of premorbid intelligence because school or college attendance does not, per se, signify that learning is taking place.

The lack of a negative correlation between premorbid I.Q. and between search errors for the controls may be explained as being due to small numbers in this group. Indeed a histogram did reveal a negative association between these variables which supports this suggestion.

There was no association between clinical variables and either strategy score or between search errors on the spatial working memory test. This finding is consistent with previous studies of schizophrenia using the CANTAB battery (Pantelis et al. 2001; Elliott et al., 1998), but is inconsistent with other investigations using different stimuli (Okada, 2001; Park et al. 1999; Carter et al. 1996). Carter et al. (1996) found a positive association between errors made on a computerised spatial working memory task and the patient's level of negative symptoms. A similar finding was reported by Park et al. (1999), although in this study the association between negative symptoms and spatial working memory was inconsistent over time. In addition, Okada (2001) found that chronic schizophrenic patients were impaired on a
novel spatial working memory task compared to a group who were in remission. This suggests that symptom display does play a role in spatial working memory performance. Aside from explanations to do with differences in patient samples, perhaps one explanation for these conflicting findings is that studies have used different methods of investigating spatial working memory. All studies that have used the CANTAB test of spatial working memory have found no association between performance and symptoms, whereas all studies that have used other methods have found associations. Perhaps the different tests may not be tapping precisely the same aspect of spatial working memory.

4.3 Visual recognition memory

Pattern and spatial recognition

These tests assess the ability of subjects to recognise previously seen shapes, or to recognise the location where shapes have been presented previously. On the pattern recognition test the performance of the schizophrenic group was significantly below that of controls (77% vs. 88%). This level of performance does suggest a problem with pattern recognition in schizophrenia, and previous studies with this patient group using the CANTAB battery have also found significant impairments on this test compared to controls (Hutton et al. 1998; Elliot et al. 1995; 1998). Indeed, previous studies have indicated that deficits in pattern recognition are present in schizophrenic patients at first onset (Hutton et al. 1998) and also in those with preserved intellectual function (Elliot et al., 1998).

In terms of spatial recognition, a similar pattern of performance was observed with the schizophrenic group successfully recognising the locations of fewer stimuli than the control group (69% vs. 83%). Again, this finding concurs with previous studies using the same test (Hutton et al. 1998; Elliot et al. 1995; 1998) and like the pattern recognition deficit, this
impaired is present in first onset schizophrenics (Hutton et al. 1998) and also in those without any global intellectual impairment (Elliot et al., 1998).

Apart from a poorer performance than controls on both tests, the current study demonstrated an important qualitative difference between the patients' performance and that of the controls; Patients performed significantly better on the pattern recognition test than on the spatial recognition test. This finding was not observed in the control group, who although they performed better on the pattern recognition test than on the spatial recognition test, this difference did not reach statistical significance. Even in a secondary analysis using a subgroup of schizophrenics who were well matched with controls on pattern recognition performance and were of roughly equal numbers to the controls, there was still a significant difference between their performance on the two tests. Although previous studies using the same tests have not drawn attention to this apparent dissociation, large differences between the performance of schizophrenic patients on the pattern recognition test and spatial recognition test have been reported (Hutton et al. 1998; pattern recognition 83% vs. spatial recognition 67%: Elliot et al. 1998; pattern recognition 80% vs. spatial recognition 66%). Indeed, the study by Elliot et al (1998) only included schizophrenic patients with preserved intellectual function which suggests that the poor performance on the visual memory battery, and the dissociation between the two tests, are not a result of global intellectual impairment, but rather are a feature of the disorder itself.

In spite of the fact that visual recognition memory deficits are present in schizophrenia, few attempts have been made to explain these deficits, either in cognitive or physiological terms. The following discussion suggests some possible reasons why schizophrenic patients perform poorly on tasks of pattern and spatial recognition.
a) An eye movement disorder?

One possible explanation of the deficit in pattern and spatial recognition relates to the initial visual processing of the image, or image location, at the presentation stage of the task. Abnormalities in eye movements have been repeatedly observed in schizophrenia with patients exhibiting a low number of eye fixations, a long fixation time, a narrow scanning range, and a fixation on irrelevant stimuli compared to controls (Phillips & David 1998; Ishizuka et al. 1998; Matsushima, 1988; Moriya, 1979). Indeed, these abnormalities have been reported for stimuli such as simple geometric figures, similar to the patterns in the pattern recognition task, as well as for more complex visual material such as drawings, story drawings and sentences, as well as for faces (Ishizuka et al. 1998; Phillips & David 1997). Therefore, schizophrenic patients may perform poorly on the pattern recognition and spatial recognition task due to inadequate initial visual processing which affects their later recognition. In addition, abnormalities in eye movement may explain why schizophrenic patients perform significantly worse on the spatial recognition test than on the pattern recognition test. On the spatial recognition test the stimuli appear randomly on any part of the computer screen, whereas in the pattern recognition test the patterns always appear in the centre of the screen. Therefore, in order to perform well on the spatial recognition task the scanning range has to be much wider to encompass the whole computer screen, and the fixation time on any one point of the computer screen has to be shorter because the subsequent stimuli that is presented may appear in a different location. Thus, it would be expected that deficits in scanning and in fixation would disproportionately affect performance on the spatial recognition test. This suggestion is also supported by a finding in the current study of a positive correlation between performance on the pattern recognition test and the spatial recognition test, as the greater the impairment in eye movement, the greater the influence on both tests.
b) a deficit in visual attention?

Schizophrenic patients have been shown to be impaired on tasks of visual attention, particularly in studies involving the antisaccade task (e.g., Maruff et al., 1996; Clementz et al. 1994; Fukushima et al., 1988). An antisaccade task involves a subject making an eye movement in the opposite direction to that of a briefly presented peripheral target. In order to perform this task successfully the subject must suppress the reflex to look toward the target, but instead utilise the target's visual information in order to shift their gaze to a contralateral location in the opposite visual field (e.g., Currie et al. 1991; Guitton et al. 1985). Patients with schizophrenia have difficulty with this task because they are unable to override the reflex to look at the peripheral target and subsequently make more antisaccade errors than controls. In addition, schizophrenics are significantly slower than controls even when correct antisaccades are made. Explanations of this deficit have been proposed to involve problems in working memory with patients being unable to shift saccades away from compelling visual stimuli (Goldman-Rakic, 1987). However, recently Maruff et al. (1996) have explained this deficit in terms of difficulties in the overt redirection of attention. Deficits in the conscious redirection of attention may offer an explanation for the schizophrenic patients' poor performance on the spatial recognition test, because this task involves the constant redirection of attention to different locations on the computer screen. If the schizophrenic patients are impaired in visual attention shifting then visual attention may linger on the site of a previously presented stimulus and not shift quickly enough to a current stimulus for adequate visual processing. Indeed, findings of increased latency in tasks involving the shifting of visual attention suggest that this might be the case (Maruff et al. 1996), and this problem will be compounded by the limited time that each stimulus in the spatial recognition task is displayed. However, explanations of visual attention deficits will not easily explain the impairment in pattern recognition in schizophrenia, as all stimuli for this task are presented in the same location on the computer screen and no visual attention shifting is required.
c) an early visual processing deficit?

There is considerable evidence that early visual information processing is impaired in schizophrenia (Braff & Sacuzzo, 1981; Knight, 1992b, 1993; Knight & Silverstein, 1998; Nuechterlein & Dawson, 1984). Explanations for this deficit follow the framework of a two stage model of early visual processing (Loftus et al. 1988; Long, 1980; Phillips, 1974; Potter, 1976). Stage 1 lasts approximately 100 ms and is where object representations are built up from the holistic analysis of stimulus components. Stage 2 lasts at least 500 msec and is where the consolidation of perceptual information takes place as a prerequisite for long term storage and for subsequent decisions regarding stimulus familiarity (Potter 1976). Stage 2 is also concerned with the allocation of attentional and conceptual resources. Of these two stages, the majority of evidence suggests that stage 1 is unimpaired in schizophrenia but that stage 2 is impaired (Knight, 2000; Knight & Silverstein, 1998). Indeed, several studies have reported evidence to suggest that impairments in stage 2 processing lead to impaired feedback to stage 1 and this is the cause of the perceptual processing deficits in schizophrenia (Rabinowicz et al. 1996; Silverstein et al. 1996a;1996b). An impairment at the stage of processing where perceptual information is consolidated in short term visual memory, for either long term storage or to facilitate familiarity judgements, would clearly lead to an impairment on visual recognition memory tasks. Adequate memory representations would not be formed and the subjects would simply not recognise some stimuli they had seen before.

d) a deficit in transient visual processing?

Another early visual processing deficit that might explain the recognition memory problems observed in the current study stems from a model of early visual processing that suggests that there are two distinct but parallel channels responsible for processing visual information (Breitmeyer & Gantz, 1976). One channel is specific to briefly presented, low spatial frequency visual information, and performs the function of orienting attention to the presence
of a stimulus. The other channel is specific to stimuli maintained over a longer period of time and performs functions including object recognition and the orientation of attention for semantic identification. These distinct channels were termed the transient and sustained channels respectively and are subsumed by two distinct types of ganglion cells in the peripheral and foveal regions of the eye (Robson & Enroth-Cugell, 1966).

In schizophrenia, there is evidence that the transient channel is impaired, and this evidence stems from a number of experimental paradigms using a variety of tasks including: the perceptual span task (Neale, 1971; Asarnow et al. 1977); backward masking (Merritt & Balogh 1989; Schuck et al. 1989); visible persistence (Schwartz et al. 1989; 1992) and electrophysiological studies (Schwartz et al. 1983). Indeed, Schwartz et al. (1999) devised an experimental paradigm that was able to assess the integrity of the transient and sustained channels respectively and found an impairment of the transient channel, consistent with previous research. The integrity of the transient channel is considered essential for a number of information processing tasks, including rapid stimulus presentation and gross feature processing (Schwartz et al. 1999).

In terms of the current study, any deficit in gross feature processing may affect the encoding of the stimulus representation in memory, and subsequently impair recognition. This might explain the poor performance of the schizophrenic group on the pattern recognition test. In terms of the spatial recognition task, rather than an impairment in feature recognition affecting performance, the problem may stem from a difficulty in orienting attention to the location of the stimulus. Both feature processing and stimulus orientation are proposed to be tasks undertaken by the transient channel, and therefore it could be argued that the deficit in pattern recognition and spatial recognition in the current study stem from an impairment in this domain of information processing.
e) an impairment of the visuo-spatial scratchpad?

Within the working memory model proposed by Alan Baddeley (1981, 1986) there are modality specific slave systems that are necessary for the maintenance and manipulation of specific types of information in memory. The visuo-spatial scratchpad is the slave system that is specific to visual material, and has been postulated to contain two subsystems; a passive store responsible for the retention of static visual material, and a store that is specialised for maintaining movement or temporal properties of spatial stimuli by means of active rehearsal. For a stationary image it is only the passive store that would be utilised, but for stimuli that are moving - then the spatial rehearsal mechanism would be implicated. In terms of schizophrenia, Fleming et al. (1997) found that schizophrenic patients were impaired on both components of the visuo-spatial scratchpad - the passive store for retaining static visual material, and the active store for retaining dynamic properties. It is obvious how a deficit in the passive store may result in an impairment in pattern recognition as the subject would simply be unable to retain the patterns that are presented to them. However, it is unclear how any impairment on the visuo-spatial scratchpad might result in an impairment in spatial recognition. Perhaps the fast presentation rate of the spatial stimuli between different locations gives the impression of movement and consequently utilises the active store. An impairment with this store would therefore lead to inadequate performance on spatial recognition memory tasks.

Neuropathological explanations for the deficit in visual recognition memory

Although the neuropathology which underlies deficits in recognition memory will remain unclear until such deficits are clearly understood on a cognitive level, some brain regions have been implicated. In normal subjects, neuro-imaging studies have implicated the involvement of the bilateral medial temporal lobes and prefrontal areas during the recognition
of previously seen objects, and the involvement of the thalamus, prefrontal and medial
temporal lobe areas during the recognition of new objects (Schacter et al. 1995; 1997; 1999;
Uecker et al. 1997).

Heckers et al (2000) investigated patterns of brain activity in a group of schizophrenic
patients and controls during episodic recognition of new and previously seen novel three
dimensional objects. They found that the schizophrenic patients were poorer than controls at
making correct recognition judgements (61% vs. 87%), but the false positive rate did not
differ between groups (i.e., the false recognition of previously unseen stimuli). PET data
showed a number of differences between the groups. The schizophrenic patients showed less
activation of the right thalamus and right prefrontal cortex than controls when presented with
new objects, and during the recognition of previously seen objects the schizophrenic patients
showed more activation of the left prefrontal cortex than controls. The attenuation of thalamic
activation during the recognition of novel objects suggests that thalamic function is
compromised in schizophrenia during tasks that require the recognition of, or attention to
novel visual stimuli (Heckers et al. 2000). This finding is consistent with previous research
which has demonstrated structural thalamic abnormalities in schizophrenia (Hazlett et al.
1999; Buchsbaum et al. 1996; Arciniegas et al. 1999; Andreason et al. 1994; 1996). Indeed,
several of these studies have found deficient metabolic activity in the thalamus during
cognitive tasks involving attention, learning and recall (Hazlett et al. 1999; Buchsbaum et al.
1996; Andreason et al. 1996). This data suggests that the thalamus is important for visual
recognition and that if this area is impaired then performance on tasks which require visual
recognition may be compromised.

In addition, the finding of more activation of the left prefrontal cortex than controls during the
recognition of previously seen objects is also consistent with previous research which has
shown an abnormal recruitment of the prefrontal cortex during cognitive tasks in
schizophrenia (Bertolino, 2000a; Cohen et al. 1998; Andreason, 1992; Sagawa et al. 1990;
Paulman et al. 1990; Berman et al. 1988; Weinberger et al. 1986; 1988). Indeed, studies by Manoach et al. (1999) and Frith et al. (1995) have found an increase in rCBF in the left dorsolateral prefrontal cortex which was associated with impaired performance on cognitive tasks. These findings suggest a reduced efficiency of this brain region (Heckers et al. 2000). Furthermore, although the controls activated the right prefrontal cortex during the recognition stage of the test, the schizophrenic patients activated the left prefrontal cortex. This is interesting because the right prefrontal cortex has been activated by visuospatial stimuli in episodic memory tasks, whereas the left has been activated by semantic / phonological stimuli (Wagner, 1999). The difference in strategy for the schizophrenic patients might indicate a impairment of the right prefrontal cortex, or a different strategy, or a disinhibition of left prefrontal activity that impedes normal visuospatial memory processes (Heckers et al. 2000).

**Associations between demographic variables, clinical variables and performance on the pattern and spatial recognition memory tests.**

Age correlated negatively with performance on the pattern recognition test for schizophrenic patients but not controls. This decline in performance with age might be a natural age related decline that is not observed in the control group due to low subject numbers. Indeed, published CANTAB norms do offer support for this suggestion as performance on the pattern recognition test does decline with age. However, when mean scores for the pattern recognition test are taken for each age band that is used in the CANTAB normative data, a difference in the rate of decline is observed between the schizophrenics and CANTAB norms. The schizophrenics show a decline in score of 18% between those who are less than 35 and those who are between 50 and 60 years of age. For the CANTAB controls, the equivalent decline is only 10%. Therefore this evidence indicates that the schizophrenic group, in addition to having an impairment in pattern recognition, also show an exaggerated age related decline in this ability.
However, this finding is inconsistent with one study which found that cognitive function did not decline markedly across the adult patient's life span (Hyde et al. 1994). Although Goldstein et al. (1998) did find that age correlated with performance on tests of cognition, this was only for those patients who had near normal cognitive function. In this study no correlation was observed between age and test scores for schizophrenic patients who had severely impaired cognition.

A positive correlation was observed between years of education and spatial recognition for the schizophrenic patients but not controls, and a non significant trend was observed between years of education and the pattern recognition test for this group. This finding suggests that level of education is an important indicator of neuropsychological functioning in schizophrenia, a suggestion that has some empirical support (Harvey et al. 1999; Swanson et al. 1998). However, this finding is surprising as premorbid I.Q. did not correlate with either visual memory test, yet premorbid I.Q. and years of education do correlate strongly. Perhaps the lack of correlation between premorbid I.Q. and the scores on the visual memory tests can be explained by the fact that the test of premorbid I.Q. was reliant on verbal abilities, whereas the visual memory tests were non verbal.

In terms of clinical variables, negative correlations were observed between BPRS total score and performance on both tests indicating that psychiatric symptoms do have an influence on visual recognition memory. Within the BPRS dimensions, 'thought disorder', 'withdrawal / retardation' and 'anxiety / depression' were all negatively associated with performance, although some associations were only marginally significant. However, neither Pantelis et al. (2001) nor Elliott et al. (1998) found any association between symptoms and performance on visual recognition memory tests, although these studies used markedly different samples of schizophrenic patients than the current study. Indeed, Elliott et al. (1998) used a sample of 12 schizophrenic patients who all had preserved intellectual functioning, and therefore the reliability and generalisability of these particular findings can be questioned.
Studies that have used different recognition memory tests have reported conflicting results, with some finding no correlation between recognition memory and psychiatric symptoms (Rushe et al. 1999b; Danion et al. 1999), but others finding a clear association (Paulsen et al. 1995).

In terms of the association between depression and scores on the visual memory tests, a negative correlation was observed between HDS score and performance on the pattern recognition, but not spatial recognition, test. This finding is consistent with a previous study which found that depressive symptoms and memory did correlate in a group of schizophrenic patients (Brebion et al. 2000). However, this study used a free recall task rather than a recognition task and therefore comparisons are difficult to draw. To the author's knowledge no previous studies have explored recognition memory in either depression, or in schizophrenic patients with depression.

Finally, duration of illness did not correlate with either test of recognition memory, a finding that has been reported previously (Elliot et al. 1998; Nathaniel-James et al. 1996) and which indicates that these cognitive deficits are static. Furthermore, Verdoux & Liraud (2000) propose that the static nature of the cognitive deficits in schizophrenia indirectly suggests that their origin is neuro-developmental.

### 4.4 Long-term memory

Rivermead Behavioural Memory Test (RBMT)

The performance of the schizophrenic patients on the RBMT suggests that they have a moderate impairment in long term memory. Previous studies using the RBMT have reported similar results with mean scores being either in the moderately impaired or poor range (Kelly et al. 2000; Carroll et al. 1999; Mockler et al. 1997; McKenna et al. 1990). Indeed, Byrn et al.
(1999) found that individuals at genetic risk of developing schizophrenia were impaired on the RBMT compared to controls.

Suggestions as to localisation of function for performance on the RBMT cannot be made as the test comprises a number of different sub-tests which are mediated by different brain regions. Indeed, Tamlyn et al. (1992) caution against extrapolations from the RBMT performance to neuroanatomical locations.

Associations between demographic variables, clinical variables and performance on the Rivermead Behavioural Memory test.

A negative association was found between performance on this test and age, which remained significant after controlling for illness chronicity. McKenna et al. (1990) also found a negative association between age and performance in schizophrenia, suggesting that performance does decline with increasing age. This association appears to be pathological in origin as healthy controls do not show an age related decline in performance (Wilson et al. 1985). In addition, a low positive correlation was found between years of education and performance on the RBMT. This indicates that the length of education has an influence on long term memory, a finding which has some empirical support (Swanson et al. 1998).

In terms of clinical variables, all symptom measures except 'hostility / suspiciousness' were negatively associated with performance on the RBMT. These findings are consistent with those of McKenna et al. (1990), who found that RBMT performance correlated with illness severity and length of illness. Furthermore, Tamlyn et al. (1992) reported that performance was associated with negative symptoms, a finding which is also consistent with the current data. These results suggest that the RBMT can provide a good indication of general severity of illness.
4.5 Semantic memory

Graded naming test (GNT)

The Graded Naming Test is a measure of semantic memory, a component of long term memory which contains stored representations of the meaning of words and knowledge about the world. This aspect of memory has repeatedly been shown to be disproportionately impaired in schizophrenia (Laws et al. 2000; Granholm et al. 1998; Mckay et al. 1996; Joyce et al. 1996; Chen et al. 1994; Clare et al. 1993; Allen et al. 1993). In the current study, the sample of schizophrenic patients obtained a mean score of 17 out of 30 on this test, with a range between 8 and 27. This level of scoring is below that of the normal sample in the original validation study (22.5: McKenna & Warrington, 1983), and below that of controls in a re-standardisation study (20.4: Warrington, 1997). These results confirm previous findings that semantic memory is impaired in schizophrenia.

In terms of neuropathological explanations of this deficit, the performance of schizophrenic patients is similar to that of neurological patients with left hemisphere lesions, who obtained a mean score of 15 in the original validation study (McKenna & Warrington, 1983). However, conclusions as to the anatomical locus of the impairment are complicated by recent findings that failure on the GNT could be due to either a deficit in accessing lexical representations, or to a degradation of the lexical items themselves (Laws et al. 2000). It is therefore likely that the deficit involves multiple brain regions.

Associations between demographic variables, clinical variables and performance on the Graded Naming test.

As previously mentioned, the GNT was positively associated with premorbid I.Q., which confirms its usefulness as a measure of intelligence. In terms of associations between clinical
variables and performance, the BPRS dimension 'withdrawal / retardation' was negatively correlated with GNT score. An association between negative symptoms and semantic memory has not been previously reported in the literature (Tamlyn et al. 1992; Chen et al. 1994; Joyce et al. 1996), although there is some evidence that performance on this type of test decreases with general severity of illness (McKay et al. 1996). In addition, indirect evidence for an association between symptoms and semantic memory was reported by Rossell et al. (1998) who found that schizophrenic patients' performance on a sentence verification task was influenced by how much the sentence was congruent with patients' delusions. For example, if the sentence was 'walls have eyes', schizophrenic patients with delusions relating to being watched were more likely to say that the sentence was true than patients with dissimilar delusions. Clearly any association between clinical symptoms and semantic memory is not straightforward, and requires a great deal more investigation.

4.6 Attention

ID / ED test

This is a test of attentional set shifting. The patients did not differ significantly from the controls in terms of stage reached, number of errors made at the ED shift, or number of errors made prior to the ED stage of the test. Nevertheless, a significant difference was observed between the patients and controls in terms of the total number of errors made at all stages of the test (39 vs. 20). This difference remained marginally significant after controlling for multiple testing. However, it is likely that this significant result is due to the control group performing exceptionally well on this aspect of the test because they made approximately 10 fewer errors than both the patients and the healthy sample used for the CANTAB norms (31). This suggests that rather than the patient sample being exceptionally poor on this performance indicator, the control group used in the present study were exceptionally good.
The critical aspect of the ID/ED test occurs at the ED shift stage of the test which is considered to be equivalent to the category shift in the WCST. The number of errors made at this stage are considered the key determinant of attentional set shifting ability (Fray et al. 1996). Previous studies using the CANTAB ID/ED test have found a significant impairment at the EDS stage of the test in schizophrenic patients compared to controls (Pantelis et al. 1999; Hutton et al. 1998; Elliot et al. 1995; 1998). Even first episode schizophrenic patients (Hutton et al. 1998), and those with preserved intellectual function (Elliot et al. 1998), have great difficulty at this stage of the test. These findings concur with studies that have used more traditional methods of investigating attentional set shifting, such as the WCST (Perry et al. 2001; Everett et al. 2001; Ilinen et al. 2000; Green et al. 1992) and the continuous performance test (Sax et al. 1998).

Detailed neurocognitive investigations of the attentional set shifting deficit in schizophrenia have suggested the problem may relate to response perseveration (Everett et al. 2001), or a failure to generalise learning (Pantelis et al. 1999). Previous suggestions that the deficit relates to an impairment in working memory have been disconfirmed (Stratta et al. 1997). Neuropathological explanations of the impairment have suggested the involvement of the dorsolateral prefrontal cortex and other structures including the limbic system (Elliott et al. 1995; Hutton et al. 1998).

Perhaps our negative finding can be explained by the fact that there was not as sharp a contrast between the performance of the schizophrenic patients and controls at this stage of the test as there were in previous studies. Hutton et al (1998) reported that 100% of their 30 controls passed the ED stage of the test compared to only 80% of patients. Similarly, Elliot et al (1995) found that all their 24 controls passed this stage compared to approximately 60% of schizophrenics. By contrast, in the current study only 12 of the 19 controls used (63%) successfully passed the EDS stage of the test compared to approximately 50% of the schizophrenics. This is a surprising finding as the controls used in the current study were...
similar to those used in the previous two studies in terms of mean I.Q., although the mean age of the controls in the current study was similar to that of those used in the study by Elliot et al. (1995), but not that of the controls used by Hutton et al (1998).

One observation that may have had a bearing on this issue relates to the instructions that are given for the ID/ED test. These mention that the subject has to learn a rule relating to the patterns. Several controls in the current study did not achieve criterion for the EDS stage of the test because they thought that this rule either related to the placement of the shapes in the four possible locations, e.g., each pattern that appears in the top centre is correct, or was related to an increased frequency with which the rule was changed. Therefore some subjects were exploring competing hypotheses about the rule, but did not guess the right one. In consequence, it can be argued that failure at the EDS stage does necessarily reflect a deficit in attentional set shifting, but may also reflect the fact that the subject has intact or even strong attentional set shifting abilities and is able to test competing hypotheses, but fails to work out the correct rule. However, even when bearing in mind this issue, it is still unclear why no controls in other studies exhibited similar problems. Perhaps there were differences in the communication between the examiners and the controls in the different studies that could explain this discrepancy.

Despite no significant difference being found between the schizophrenic patients and controls at the EDS stage of the task in this particular study, only 52% of the schizophrenic patients successfully passed this stage of the task. This is a lower percentage than that found by Hutton et al (1998; 80%) and Elliot et al. (1995; 60%). This difference may be explained by variations between the samples used in these studies. Hutton et al. (1998) used a sample of first episode schizophrenics who had a mean premorbid I.Q. of 109, and Elliott et al. (1995) studied a sample of schizophrenics with preserved intellectual function who had a mean premorbid I.Q. of 110. In the current study, a large cross sectional sample of schizophrenic patients was used who had a mean I.Q. of 98. In addition, more schizophrenic patients were
examined in the current study (48) than in the previous two studies (Elliot et al. 1995; 32: Hutton et al. 1998; 30), and therefore the current study used a more representative sample containing a greater range of abilities.

**Associations between demographic variables, clinical variables and performance on the ID/ED test.**

Premorbid I.Q. correlated negatively with errors at ED shift for schizophrenic patients but not for controls. This association was not found in previous studies which have used the CANTAB (Elliott et al. 1995), although performance on some aspects of the test were negatively associated with premorbid I.Q. in the study by Pantelis et al. (1999). This finding appears specific to schizophrenia because neither data from the controls in the current study, nor from CANTAB norms, suggest any association between I.Q. and performance on the ID/ED test.

Stage reached on the ID / ED test was negatively correlated with BPRS total, and the symptom dimensions ‘thought disorder’ and ‘withdrawal retardation’. Of these associations, by far the strongest was between ‘withdrawal / retardation’ and stage reached. This finding suggests that the greater the severity of negative symptoms, the poorer the performance on the ID/ED test. In relation to previous CANTAB studies, Elliott et al (1998) found no association between symptoms and performance on any aspect of the ID/ED test, whereas Pantelis et al (1999) found a strong negative correlation between performance at the simple discrimination reversal stage of the test and negative symptoms. They also reported that schizophrenic patients who failed to make the ED shift had higher levels of negative symptoms than those who succeeded. Taken together with the results of the current study, the findings of Pantelis et al. (1999) suggest that prominent negative symptoms impair the ability of patients to perform successfully on tests of attentional set shifting. These results are consistent with many studies.
which have found negative associations between performance on the WCST and the presence of negative symptoms (Elliott & Sahakian, 1995; Pantelis et al. 1992; Berman et al. 1997; Norman et al. 1997). This association confirms pre-existing notions that both negative symptoms and performance on attentional set shifting tasks are mediated by the dorso-lateral prefrontal cortex.

4.7 Planning ability

Stockings of Cambridge

This test contains multiple performance indices but in a general sense it assesses the ability of a subject to plan and think ahead during the execution of a novel task. Performance can be examined in terms of the number of problems that the subject solves using the fewest moves possible (minimum move solutions), the thinking time prior to initiating movement on each stage of the task (initial thinking time), and the thinking time during the execution of each task (subsequent think time). In the present study, the schizophrenic group solved fewer problems using the minimum number of moves than the control group (6.9 vs. 9.1). The group difference remained significant after controlling for multiple testing. This finding has been reported in previous studies which have used the same test (Pantelis et al. 1997; Hutton et al. 1998), and Elliott et al. (1998) found a trend for significance on this measure with intellectually preserved schizophrenic patients performing more poorly than controls. Studies using other versions of the Stockings of Cambridge task have also reported similar findings (Perry et al. 2001; Rushe et al. 1999a; Bustini et al. 1999; Morris et al. 1995; Morice & Delahunty, 1996), and it seems that only one study has reported normal schizophrenic performance on this type of task (Krabbendam et al. 1999).

An impairment in terms of minimum move solutions on the Stockings of Cambridge test might reflect a failure to consider each solution adequately before attempting it, and as a
consequence each problem is not solved with maximum efficiency (Hutton et al. 1998). This explanation is supported by the current findings that the schizophrenic patients had significantly faster initial thinking times than controls on most stages of the test.

Another possible contribution to the deficit in minimum move solutions may relate to short term visuo-spatial memory. In order to solve each problem the subject must retain a planned sequence of moves in mind whilst executing the task. Perhaps the deficit in spatial span that was observed for the schizophrenic group impairs this process, with patients being unable to hold in mind the moves necessary to solve each problem. However, this explanation is not supported by the evidence as no significant correlation was found between spatial span and minimum move solutions (r=.22; n=53; p=.10).

Another possible explanation relates to visuo-spatial working memory. It may be that the ability to manipulate information that is held in mind is impaired which results in problems performing cognitive operations such as those needed for the Stockings of Cambridge test. Indeed, this explanation has some support in the current study as a moderate negative correlation was found between minimum move solutions and between search errors on the spatial working memory test (r=-.48; n=53 p<.0005). Thus, it appears that the schizophrenic patients' inability to solve the problems on the Stockings of Cambridge test with maximum efficiency is due to a combination of two factors; an inability to consider solutions sufficiently before attempting them, and an inability to perform cognitive operations on the information that is held in mind.

In terms of initial and subsequent thinking times on the Stockings of Cambridge test, the finding of decreased initial thinking times and increased subsequent think times at some stages of the task has been reported in a previous study (Hutton et al.1998). In line with the earlier suggestion, these results imply that the schizophrenic group initiate solutions to a problem before they have been fully planned and as a consequence they have to pause during
the task for further planning and to redress their errors (Pantelis et al. 1997; Hutton et al. 1998). However, this suggestion does not explain why the schizophrenic patients did not utilise more subsequent thinking time than controls at the 4 and 5 move problem stage, nor indeed why their composite subsequent think time was comparable to that of the control group. Perhaps there is a learning effect which takes place whereby the schizophrenic patients simply get better at solving the problems after initial difficulties, and they therefore need less subsequent thinking time in the later stages of the test.

Neuropathological explanations of the schizophrenic patients' impairment on the Stockings of Cambridge test have emphasised the similarity between their pattern of performance and that of patients with frontal lobe lesions (Hutton et al. 1998; Pantelis et al. 1997). Compared to controls, frontal patients typically display a decrease in initial thinking time, an increase in subsequent thinking time, and a decrease in the number of minimum move solutions (Pantelis et al. 1997). This pattern of performance is remarkably similar to that obtained with schizophrenic populations, and can be distinguished clearly from the pattern of performance obtained from other patient groups. For example, Parkinson's disease patients show prolonged initial thinking times, and patients with temporal lobe lesions are unimpaired in terms of minimum move solutions (Pantelis et al. 1997). Indeed, within the wider literature many comparisons have been made between the neuropathology of schizophrenia and that of patients with frontal lobe lesions (e.g., Owen et al. 1990).

However, Morris et al. (1995) suggest that the planning deficit in schizophrenia may not be explained purely in terms of damage to the prefrontal cortex. There are many structural and neurochemical abnormalities that are observed in the disorder and these are not restricted to the frontal lobes. Perhaps the impairment can be considered as being due to damage to a corticostriatal loop subserving cognition instead of a specific region. One candidate cognitive loop involves the dorsolateral prefrontal cortex, the dorsolateral caudate nucleus, the globus pallidus and the thalamus. Indeed, previous findings of overall slowness on the Stockings of
Cambridge test (Pantelis et al. 1997) are consistent with the idea that subcortical structures or frontal-striatal-thalamic circuits are involved in the neuropathology of the disorder (e.g., Robbins, 1990; Buchsbaum et al. 1992; Pantelis et al. 1992).

Associations between demographic variables, clinical variables and performance on the Stockings of Cambridge test

For the schizophrenic group, age was positively associated with initial think time for 2 move problems, and subsequent think times for 4 and 5 move problems respectively. These results suggest that age does influence performance to some extent, particularly in terms of subsequent think times on the more difficult stages of the task. However, previous studies using this type of test have not found any association between age and performance (Pantelis et al. 1997; Morris et al. 1995), although this may be due to lower subject numbers in these studies (for Pantelis et al., n=36; for Morris et al. n= 30). For the control group, age was negatively correlated with minimum move solutions, composite subsequent think times and subsequent think times for 4 move problems. In addition, for this group there were several associations between age and subsequent think times that were marginally significant. These results indicate a similar pattern of performance for schizophrenics and controls, with subsequent thinking time tending to increase with age.

For the schizophrenic group, no other demographic variables were associated with performance on this test. However, for the control group premorbid I.Q. was negatively correlated with subsequent think times for 2, 3 and 4 move problems. This suggests that there is an association between premorbid I.Q. and problem solving ability in the normal population, and that this association is not present in patients with schizophrenia.

Duration of illness was positively associated with initial think times for 2 move problems, composite subsequent think times, and subsequent think times for 4 move problems. These
results suggest that length of illness is associated with a decline in the speed of thought processes in problem solving tasks. However, these findings must be considered in the light of the fact that no previous studies using this type of task have found such an association (Pantelis et al. 1997; Elliott et al. 1998; Morris et al. 1995; Rushe et al. 1999a), and there is a wider body of evidence which suggests that the cognitive deficits in schizophrenia are non progressive (e.g., Verdoux & Liraud, 2000).

One study did find an association between duration of illness and performance on the Trail Making test and digit symbol test, and as these tests involve visuo-motor processes (Cuesta et al. 1998), it could be argued that they do involve similar processes to the Stockings of Cambridge test. Nevertheless, the vast majority of evidence does suggest that there is no standard temporal evolution of neuropsychological deficits in schizophrenia. Perhaps the conflicting findings indicate that cognitive decline may exist in subgroups of patients (for a review see Friedman et al. 1999b), and / or that a limited number of cognitive domains do display progressive deterioration (Cuesta et al. 1998).

In terms of symptom display and performance on the Stockings of Cambridge test, the only observed associations were between the BPRS dimensions ‘thought disorder’, ‘hostility / suspiciousness’ and subsequent think times for 5 move problems. These correlations were negative and low to moderate in degree. No previous studies have investigated the association between thinking times and symptoms in schizophrenia. Perhaps the current findings suggest that positive symptoms impinge on performance at times when considerable strain is placed upon the cognitive system. Clearly this is a tentative explanation for the current pattern of results, which needs further empirical investigation.
Chapter 5. Results over the study period

5.1 Dropouts

Between baseline and 9-month follow-up 21 (30%) of the original 70 patients recruited for the study were lost to follow-up. Of these, 13 refused to be seen again by the research team, 4 had relapsed and were too ill to be seen, 3 had moved out of the area and were not contactable, and one died. Between 9-month and 18-month follow-up a further 18 (26%) of the remaining 49 schizophrenics were discontinued, which brings the total dropout figure to 39 (56%). Of those who dropped out of the study between 9-month and 18-month follow-up, 8 patients refused contact with the research team, 7 patients changed medication and were no longer suitable for the study, 2 patients were symptom free and no longer on antipsychotic medication, and 1 person died. A breakdown of the reasons why patients failed to complete the study is shown in Chart 5.1. The patients who dropped out of the study did not differ on any variable from those who continued (see Appendices A.1 & A.2).

*Chart 5.1 Why patients failed to complete the study*
5.2 Associations between changes in symptoms and changes in cognition over the study period

Few associations were found between changes in symptoms and changes in performance on the cognitive tests. However, the symptoms of 'withdrawal / retardation' were negatively associated with performance on the Stockings of Cambridge test in terms of composite initial thinking times ($r=-.52; n=24; p=.008$), initial thinking times for 4 move problems ($r=-.53; n=25; p=.006$), and initial thinking times for 5 move problems ($r=-.43; n=24; p=.036$). In addition, subsequent thinking times for 5 move problems were also negatively correlated with these symptoms ($r=-.50; n=24; p=.013$). Furthermore, negative correlations were found between composite initial thinking times and BPRS total score ($r=-.62; n=24; p=.001$) and the symptom dimensions, 'thought disorder' ($r=-.53; n=24; p=.007$) and 'hostility / suspiciousness' ($r=-.52; n=24; p=.009$). Finally, although digit span changes did positively correlate with changes on both the BPRS total score ($r=.40; n=26; p=.038$) and the BPRS dimension 'anxiety / depression' ($r=.60; n=26; p=.001$), an examination of the respective scatterplots did not suggest a linear trend. (see Appendix A.3).

5.3 Comparison of performance on cognitive tests between baseline and 9-month follow-up for controls.

Between baseline and 9-month follow-up the control group did not display changes in performance on any cognitive measure except the Stockings of Cambridge test. Here, the controls showed a statistically significant decrease in thinking latency for composite initial think time (7203 vs. 5094 msec; $t=2.98$ with 15 df, $p=.009$), composite subsequent think time (817 vs. 345 msec; $t=2.20$ with 13 df, $p=.046$), and initial think times for 3 move problems (5208 vs. 3504 msec; $t=3.00$ with 15 df, $p=.009$). In addition, the trend for controls to utilise
less thinking time at 9-month follow-up compared to baseline was repeated throughout the Stockings of Cambridge test (see Appendix A.4).

5.4 Typical vs. Atypical groups – comparing performance over the study period

i) Baseline Comparisons

For baseline comparisons there were between 4 and 7 patients in the typical group and between 30 and 44 patients in the atypical group. The mean age of the typical group was 41, with a premorbid I.Q. of 104. The atypical group had a mean age of 34 and a premorbid I.Q. of 98. The groups were comparable on demographic variables (p>.10 for all measures) at baseline. However, in terms of clinical variables differences were found for BPRS ratings of 'withdrawal / retardation' where the typical group scored less on this dimension than the atypical group (1.2 vs. 4.0; t= 2.39 with 12 df, p=.033). Group differences were also observed on the HDS with the typical group scoring higher than the atypical group (15 vs. 9; t=-2.17 with 48 df, p=.035).

In terms of cognition, the groups were comparable on all measures except the Stockings of Cambridge test. Firstly, there was a marginally significant difference in initial thinking times for 3 move problems with the typical group exhibiting shorter latencies than the atypical group (2259 vs. 5625 msec; t=1.98 with 33 df, p=.055). Secondly, the groups differed at baseline for composite subsequent think times with the typical group again exhibiting shorter latencies than the atypical group (634 vs. 1006 msec; t=2.80 with 20 df, p=.011). Thirdly, the same pattern was observed for subsequent think times at the 3 move problem stage with the typical group utilising less thinking time than the atypical group (24 vs. 421 msec; t=3.42 with 30 df, p=.002: see Appendix A.5 i).
ii) A comparison of changes in clinical symptoms and cognitive performance between baseline and 9-month follow-up

For these comparisons the numbers of subjects in the typical group varied between 3 and 7, whilst the numbers in the atypical group varied between 28 and 41. No significant differences were observed between the groups in terms of changes in clinical symptoms between baseline and 9-month follow-up (p>.26 for all measures). For the cognitive data the only group difference was on the digit span test where the atypical group improved in performance between baseline and 9-month follow-up whereas the typical group showed no change (+.27 vs .00; t=2.17 with 32 df, p=.037: see Appendix A.5 ii).

iii) A comparison of clinical symptoms and cognitive performance at 9-month follow-up

For these comparisons the numbers in the typical group varied between 3 and 7, whilst numbers in the atypical group were between 31 and 41. No statistically significant differences in symptoms were observed at 9-month follow-up between schizophrenic patients on typical antipsychotics and those on atypical antipsychotics (p>.083 for all measures).

For the cognitive data, the only differences between the groups at 9-month follow-up were on the ID/ED test and the Stockings of Cambridge test. On the ID/ED test the patients on atypical antipsychotics performed better than those on typical antipsychotics in terms of stage reached (7.9 vs. 7.0; t=5.68 with 35 df, p<.0005). This difference remained significant after baseline scores were controlled for (F= 9.85, p<.0005). On the Stockings of Cambridge test, the typical group achieved more minimum move solutions than the atypical group (9.5 vs.

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20 As only 1 patient in the typical group completed the study, no comparisons between the typical and atypical groups could be made at 18-month follow up.
7.3; \( t = -2.09 \) with 40 df, \( p = .043 \). Again, when baseline scores were covaried out the group difference remained (\( F = 4.52, p = .016 \); see Appendix A.5 iii).

5.5 High 5HT-2A affinity group (risperidone, olanzapine, clozapine) vs. low 5HT-2A affinity group (quetiapine, amisulpride) – comparing performance over the study period.

i) Baseline comparisons

For these comparisons at baseline the numbers in the high 5HT-2A affinity group varied between 22 and 29, whilst there were between 7 and 15 patients in the low 5HT-2A affinity group. The mean age of the high 5HT-2A affinity group was 33 and they had a premorbid I.Q. of 98. The low 5HT-2A affinity group had a mean age of 37 and a premorbid I.Q. of 97. No group differences were found at baseline on demographic variables (\( p > .14 \) for all measures) or clinical measures (\( p > .27 \) for all measures). For the cognitive tests the only significant difference between the groups at baseline was on the ID/ED test. Here, the schizophrenics on high 5HT-2A affinity antipsychotics reached a higher stage than those on low 5HT-2A affinity antipsychotics (8.2 vs. 7.0; \( t = 2.70 \) with 31 df, \( p = .011 \); see Appendix A.6 i).

ii) Comparison of changes in clinical symptoms and cognitive performance over the study period

For comparisons of change between baseline and 9 month follow up there were between 15 and 27 patients in the high 5HT-2A affinity group, and between 8 and 14 patients in the low 5HT-2A affinity group. For comparisons between baseline and 18 month follow up the numbers were slightly reduced, with between 13 and 20 patients in the high 5HT-2A affinity
group, and between 6 and 10 in the low 5HT-2A affinity group. The number of patients in each group for a particular comparison can be found in appendix A.6.

In terms of group differences in symptom changes between baseline and 9-month follow-up, the schizophrenics on high 5HT-2A affinity antipsychotics showed a greater reduction in BPRS measures of anxiety / depression than those on low 5HT-2A affinity antipsychotics (-2.4 vs. -0.2; t=-2.47 with 39 df, p=.018). No other differences in symptom change were found between the groups between baseline and 9-month follow-up. Between baseline and 18-month follow-up no group differences in symptom change were observed (p>.10 for all measures).

Several statistically significant differences were observed between groups in terms of changes in cognitive performance between baseline and 9-month follow-up. Firstly, a marginally significant group difference was observed on the digit span test with the schizophrenic patients on low 5HT-2A affinity antipsychotics showing an improvement, whereas the group on high 5HT-2A affinity antipsychotics showed no change (+0.5 vs. 0.0; t=-1.95 with 31 df, p=.059). Secondly, the low 5HT-2A affinity group showed an improvement in performance on both visual recognition memory tests whereas the performance of the high 5HT-2A affinity group worsened on both tests (see Table 5.1 below).

*Table 5.1. There was a contrast between the groups in terms of changes in performance on the visual recognition memory tests.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (N)</th>
<th>Change between baseline &amp; 9-month follow-up</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>sd</td>
</tr>
<tr>
<td>Pattern recognition</td>
<td>High 5HT-2 (22)</td>
<td>-3.9</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>Low 5HT-2 (13)</td>
<td>7.0</td>
<td>15.3</td>
</tr>
<tr>
<td>Spatial recognition</td>
<td>High 5HT-2 (23)</td>
<td>-6.7</td>
<td>17.8</td>
</tr>
<tr>
<td></td>
<td>Low 5HT-2 (13)</td>
<td>6.5</td>
<td>10.4</td>
</tr>
</tbody>
</table>
Thirdly, on the Stockings of Cambridge test initial think times for 2 move problems showed a
decrease for the low 5HT-2A affinity group whereas a latency increase was observed for the
high 5HT-2A affinity group (-600 vs. +496 msec; \( t=2.66 \) with 30 df, \( p=.012 \)). Fourthly, in
terms of subsequent think times the low 5HT-2A affinity group showed a larger decrease in
composite latencies than the high 5HT-2A affinity group (-531 vs. -68 msec; \( t=2.08 \) with 28
df, \( p=.047 \)). Finally, for subsequent think times at the 5 move problem stage the low 5HT-2A
affinity group showed a decrease in latency whereas the high 5HT-2A affinity group showed
an increase (-827 vs. +126 msec; \( t=2.48 \) with 29 df, \( p=.019 \): see Appendix A.6 ii).

Between baseline and 18-month follow-up there was a significant group difference in terms of
changes in performance on the digit span test, with the low 5HT-2A affinity group improving
whereas the performance of the high 5HT-2A affinity group remained constant (+0.75 vs. 0.0;
\( t=-3.00 \) with 7 df, \( p=.020 \)). In addition, several group differences were observed on the
Stockings of Cambridge test with the high 5HT-2A affinity group tended to show an increase
in initial thinking time at most stages of the test whereas the low 5HT-2A affinity group
tended to show a decrease. These results are in Table 5.2 overleaf. (Also see Appendix A.6
iii).
Table 5.2 Between baseline and 18-month follow-up there was a general trend for the schizophrenics on low 5HT-2A affinity antipsychotics to utilise less initial thinking time on the Stockings of Cambridge test whereas the high 5HT-2A affinity group tended to utilise more.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (N)</th>
<th>Change between baseline and 18-month follow-up (msec)</th>
<th>t-tests</th>
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</thead>
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<tr>
<td>Composite initial think times</td>
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<td>sd</td>
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<td>High 5HT-2 (15)</td>
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<tr>
<td>Low 5HT-2 (6)</td>
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<tr>
<td>Initial think times 2 move problems</td>
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<tr>
<td>High 5HT-2 (16)</td>
<td>605</td>
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<td>Low 5HT-2 (7)</td>
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<td></td>
</tr>
</tbody>
</table>

iii) A comparison of clinical symptoms and cognitive performance at 9-month follow-up

For these comparisons there were between 22 and 27 patients in the high 5HT-2A affinity group, and between 10 and 14 patients in the low 5HT-2A affinity group. No significant differences in symptoms were observed at 9-month follow-up between schizophrenics on high 5HT-2A affinity antipsychotics and those on low 5HT-2A affinity antipsychotics (p>.52 for all measures).

In terms of cognition, the only differences at 9-month follow-up were on the spatial recognition test and the Stockings of Cambridge test. On the spatial recognition test the low 5HT-2A affinity group achieved a significantly higher score than the high 5HT-2A affinity group (77% vs. 64%; t=-3.92 with 30 df, p=<.0005). This difference remained significant
after baseline scores were controlled for ($F=14.1$, $p=.001$). On the Stockings of Cambridge test several differences were observed at 9-month follow-up. Firstly, the low affinity 5HT-2A group had considerably shorter initial thinking times than the high affinity 5-HT2A group for 4 move problems ($4317$ vs. $8136$ msec; $t=2.83$ with 34 df, $p=.008$). This difference remained significant after baseline scores were controlled for ($F=5.27$, $p=.029$). Secondly, for composite subsequent think times the low affinity 5HT-2A group had significantly shorter latencies than the high affinity 5HT-2A group ($661$ vs. $1190$ msec; $t=2.28$ with 32 df, $p=.029$). This difference was reduced to non significance when baseline scores were covaried out ($F=2.39$, $p=.13$). A similar pattern of results was observed for subsequent think time for 3 move problems. Here, the low 5HT-2A affinity group again had shorter latencies than the high 5HT-2A group ($119$ vs. $351$ msec; $t=2.06$ with 30 df, $p=.048$). Again, this difference was reduced to non significance when baseline scores were controlled for ($F=2.27$, $p=.14$). In general, on the Stockings of Cambridge test the low 5HT-2A affinity group utilised less initial and subsequent thinking time than the high 5HT-2A affinity group (see Appendix A.6 iv).

iv) Comparison of clinical symptoms and cognitive performance at 18-month follow-up

For these comparisons there were between 14 and 20 patients in the high 5HT-2A affinity group, and between 6 and 10 in the low 5HT-2A affinity group. No significant differences in symptoms were observed at 18-month follow-up between schizophrenic patients on high 5HT-2A affinity antipsychotics and those on low 5HT-2A affinity antipsychotics ($p>.24$ for all measures).

On the cognitive measures the only group differences at 18-month follow-up were on the Stockings of Cambridge test. Here, the low 5HT-2A affinity group utilised significantly less initial think time than the high 5HT-2A affinity group at 3, 4 and 5 problem stages (see Table 141.
5.3). The group differences at the 3 and 4 move stage remained significant after baseline scores were controlled for (p<.046 for both measures), but not when 9-month scores were taken into account (p>.92 for both measures). The group difference at the 5 move problem stage of the test was reduced to non significance when baseline scores and 9-month scores were controlled for (p>.98 for both comparisons). In addition, the low 5HT-2A affinity group utilised less composite subsequent think time than the high 5HT-2A affinity group (353 vs. 810 msec; t=2.55 with 19 df, p=.019). This difference was reduced to non significance when baseline scores and 9-month scores were controlled for (p>.13 for both comparisons: see Appendix A.6 v).

Table 5.3 At 18-month follow-up the schizophrenics on low 5HT-2A affinity antipsychotics exhibited shorter initial thinking latencies than those on high 5HT-2A affinity antipsychotics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (N)</th>
<th>Descriptive statistics</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite initial think times</td>
<td></td>
<td></td>
<td>t-value</td>
</tr>
<tr>
<td>High 5HT-2 (15)</td>
<td>5086 2353</td>
<td>1.66 19 .11</td>
<td></td>
</tr>
<tr>
<td>Low 5HT-2 (6)</td>
<td>3396 1133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial think times 2 move problems</td>
<td></td>
<td></td>
<td>0.81 21 .42</td>
</tr>
<tr>
<td>High 5HT-2 (16)</td>
<td>1948 1418</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low 5HT-2 (7)</td>
<td>1455 1133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial think times 3 move problems</td>
<td></td>
<td></td>
<td>2.18 20 .041</td>
</tr>
<tr>
<td>High 5HT-2 (16)</td>
<td>4365 1709</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low 5HT-2 (6)</td>
<td>2779 661</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial think times 4 move problems</td>
<td></td>
<td></td>
<td>2.80 21 .010</td>
</tr>
<tr>
<td>High 5HT-2 (17)</td>
<td>10204 6662</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low 5HT-2 (7)</td>
<td>4969 2472</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial think times 5 move problems</td>
<td></td>
<td></td>
<td>2.55 19 .019</td>
</tr>
<tr>
<td>High 5HT-2 (16)</td>
<td>7840 4673</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low 5HT-2 (6)</td>
<td>4241 1918</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.6 Multiple receptor blocking group (olanzapine, clozapine, quetiapine) vs. preferential dopamine blocking group (risperidone, amisulpride) - comparing performance over the study period.

i) Baseline comparisons

For these comparisons at baseline the numbers in the multi receptor blocking group varied between 18 and 28, whilst there were between 8 and 16 patients in the preferential dopamine blocking group. The mean age of the multi receptor blocking group was 33 and they had a premorbid I.Q. of 99. The preferential dopamine blocking group had a mean age of 37 and a premorbid I.Q. of 95.

No significant differences were observed between the two groups on demographic variables (p > .095 for all measures) or clinical variables (p > .17 for all measures) at baseline. However, a number of group differences were found on the cognitive measures. Firstly, on the graded naming test the preferential dopamine group scored significantly higher than the multi-receptor group (20 vs. 16; t = -2.55 with 39 df, p = .015). Secondly, on the Stockings of Cambridge test the preferential dopamine group achieved significantly more minimum move solutions than the multi-receptor group. In addition, the preferential dopamine group utilised significantly more initial thinking time than the multi-receptor group for 2 and 3 move problems. Indeed, there was a general trend for the preferential dopamine group to use more initial thinking time than the multi-receptor group on the Stockings of Cambridge test (see Table 5.4 & Appendix A.7 i).
Table 5.4. At baseline the preferential dopamine group achieved more minimum move solutions and utilised more initial thinking time than the multi-receptor group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (N)</th>
<th>Descriptive statistics</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (sd)</td>
<td>t-value, df, P</td>
</tr>
<tr>
<td>Minimum move solutions</td>
<td>Multi (17)</td>
<td>5.7 (1.5)</td>
<td>-2.71, 26, .012</td>
</tr>
<tr>
<td></td>
<td>Dopamine (11)</td>
<td>7.2 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Composite initial think times</td>
<td>Multi (21)</td>
<td>4351 (2371)</td>
<td>-1.22, 29, .23</td>
</tr>
<tr>
<td></td>
<td>Dopamine (10)</td>
<td>5598 (3195)</td>
<td></td>
</tr>
<tr>
<td>Initial think times 2 move problems</td>
<td>Multi (21)</td>
<td>1398 (1155)</td>
<td>-2.48, 28, .019</td>
</tr>
<tr>
<td></td>
<td>Dopamine (11)</td>
<td>2234 (735)</td>
<td></td>
</tr>
<tr>
<td>Initial think times 3 move problems</td>
<td>Multi (22)</td>
<td>5084 (3250)</td>
<td>-2.33, 12, .038</td>
</tr>
<tr>
<td></td>
<td>Dopamine (12)</td>
<td>12315 (10467)</td>
<td></td>
</tr>
<tr>
<td>Initial think times 4 move problems</td>
<td>Multi (20)</td>
<td>3994 (2299)</td>
<td>-1.86, 13, .086</td>
</tr>
<tr>
<td></td>
<td>Dopamine (12)</td>
<td>7317 (5924)</td>
<td></td>
</tr>
<tr>
<td>Initial think times 5 move problems</td>
<td>Multi (22)</td>
<td>5914 (4085)</td>
<td>.400, 30, .69</td>
</tr>
<tr>
<td></td>
<td>Dopamine (10)</td>
<td>5301 (3841)</td>
<td></td>
</tr>
</tbody>
</table>

ii) A comparison of changes in clinical symptoms and cognitive performance over the study period

For comparisons of change between baseline and 9 month follow up there were between 17 and 26 patients in the multi receptor blocking group, and between 8 and 15 patients in the preferential dopamine blocking group. For comparisons of change between baseline and 18 month follow up there were between 11 and 20 patients in the multi receptor blocking group, and between 6 and 10 in the preferential dopamine blocking group. The number of patients in each group for a particular comparison can be found in appendix A.7.

No significant differences were observed between the groups in terms of changes in clinical symptoms between baseline and 9-month follow-up (p>1.0 for all measures), or between baseline and 18-month follow-up (p>.071).
There was only one significant difference between the groups in terms of changes in cognitive performance between baseline and 9-month follow-up. On the Stockings of Cambridge test the preferential dopamine group exhibited a decrease in subsequent think time for 2 move problems whereas the multi-receptor group exhibited an increase (-267 vs. +57 msec; t=2.41 with 28 df, p=.023: see Appendix A.7 ii).

Between baseline and 18-month follow-up there were several statistically significant group differences. On the RBMT the multi receptor blocking group improved in performance whereas the preferential dopamine group showed a decrement (+0.9 vs. -2.2; t=2.85 with 20 df, p=0.10). On the spatial span test the multi receptor blocking group improved in performance whilst the preferential dopamine group remained constant (+1.0 vs. 0.0; t=2.14 with 24 df, p=.042). In addition, on the Stockings of Cambridge test the multi receptor blocking group increased in initial thinking time for 5 move problems, whereas the preferential dopamine group showed a latency decrease (+271 vs. -1430 msec; t=2.43 with 19 df, p=.025: see Appendix A.7 iii).

iii) Comparison of clinical symptoms and cognitive performance at 9-month follow-up

For these comparisons there were between 21 and 26 patients in the multi receptor blocking group, and between 10 and 15 patients in the preferential dopamine blocking group. No statistically significant differences were observed between the groups on clinical variables at 9-month follow-up (p>.33 for all measures). In terms of cognition, at 9-month follow-up the only group difference was on the graded naming test where the dopamine group achieved a higher score than the multiple receptor group (16 vs. 19; t=-1.98 with 38 df, p=.054). However, this difference was present at baseline and therefore reflects a pre-existing
difference rather than a medication effect. Indeed, when baseline scores are controlled for, the group difference disappears (F=2.50, p=.12; see Appendix A.7 iv).

iv) A comparison of clinical symptoms and cognitive performance at 18-month follow-up

For these comparisons there were between 13 and 20 patients in the multi receptor blocking group, and between 7 and 10 patients in the preferential dopamine blocking group. No statistically significant differences were observed between the groups on clinical variables at 18-month follow-up (p>.31 for all measures). Apart from the (pre-existing) difference in performance on the graded naming test (t=-3.35 with 24 df, p=.003), the only group difference at 18-month follow-up was on the Stockings of Cambridge test. Here, the preferential dopamine group utilised significantly more initial think time for 2 move problems than the multi receptor blocking group (3163 vs. 1228 msec; t=-3.16 with 9 df, p=.011). This difference remained when both baseline scores and 9-month scores were controlled for (p=.025 for both tests: see Appendix A.7 v).

5.7 Fast dopamine D2 dissociating group (clozapine, quetiapine, amisulpride) vs. slow dopamine D2 dissociating group (olanzapine, risperidone) - a comparison of performance over the study period.

i) Baseline comparisons

For these comparisons at baseline the numbers in the fast dopamine D2 dissociating group varied between 17 and 26, whilst there were between 13 and 18 patients in the slow dopamine D2 dissociating group. The mean age of the fast dopamine D2 dissociating group was 34 and they had a premorbid I.Q. of 101. The slow dopamine D2 dissociating group also had a mean age of 34 and a premorbid I.Q. of 92.
The fast dopamine D2 dissociating group had a significantly higher premorbid I.Q. than the slow dopamine D2 dissociating group (101 vs. 92; t=2.18 with 42 df, p=.035). No group differences were observed in terms of age or years of education (p>.53). For clinical variables no group differences were observed (p>.086 for all measures). The only difference between the groups on cognitive measures occurred on the Stockings of Cambridge test. Here, the fast dopamine D2 dissociating group utilised marginally less subsequent thinking time than the slow dopamine D2 dissociating group at the 3 move problem stage (203 msec vs. 966 msec; t=-2.15 with 28 df, p=.040: See Appendix A.8 i).

\[ i \) A comparison of changes in clinical symptoms and cognitive performance over the study period

For comparisons of change between baseline and 9 month follow up there were between 13 and 24 patients in the fast dopamine D2 dissociating group, and between 9 and 17 patients in the slow dopamine D2 dissociating group. For comparisons of change between baseline and 18 month follow up there were between 12 and 19 patients in the fast dopamine D2 dissociating group, and between 6 and 11 in the slow dopamine D2 dissociating group. The number of patients in each group for a particular comparison can be found in appendix A.8.

No statistically significant differences were observed between the groups in terms of changes in symptom ratings between baseline and 9-month follow-up (p>.15 for all measures).

However, a group difference did emerge when comparisons were made between baseline and 18-month follow-up. On the BPRS dimension ‘withdrawal / retardation’ the slow dopamine D2 dissociating group exhibited a greater decrease in symptoms than the fast dissociating group (-4.0 vs. -1.0; t= 2.32 with 28 df, p=.028). No other clinical differences were observed. Between baseline and 9-month follow-up the only statistically significant group difference between the groups on cognitive measures was on the pattern recognition memory test. Here, the fast dopamine D2 dissociating group showed an improvement in performance whereas the
slow dopamine D2 dissociating group showed a decrement (+5% vs. -8%: t=2.70 with 33 df, p=.011). This difference remained marginally significant after controlling for the difference in premorbid I.Q. (F=3.88, P=.057). In addition, a marginally significant group difference was observed in terms of total errors on the ID / ED test. This difference was due to the fast dopamine D2 dissociating group showing an increase in total errors between baseline and 9-month follow-up, whereas the slow dopamine D2 dissociating group showed a decrease in total errors (+2% vs. -8%; t=2.01 with 32 df, p=.053). However, the statistical significance of this difference decreased when premorbid I.Q. was taken into account (F=3.00, P=.093; see Appendix A.8 ii).

Between baseline and 18-month follow-up the only difference in changes between groups occurred on the Stockings of Cambridge test. Here, the fast dissociating group displayed a decrease in initial thinking time for 2 move problems whereas the slow dissociating group showed an increase (-166 vs. +1399 msec; t= -2.86 with 22 df, p=.009). This difference remained statistically significant after controlling for differences in premorbid I.Q. (F=7.76, P=.011; see Appendix A.8 iii).

iii) Comparison of clinical symptoms and cognitive performance at 9-month follow-up

For these comparisons there were between 19 and 24 patients in the fast dopamine D2 dissociating group, and between 13 and 17 patients in the slow dopamine D2 dissociating group. No significant differences in symptom ratings were observed between groups at 9-month follow-up (p>.37). For the cognitive measures, statistically significant group differences were observed on the spatial working memory test and the Stockings of Cambridge test. On the spatial working memory test the fast dopamine D2 dissociating group had a superior strategy score than the slow dopamine D2 dissociating group (34 vs. 37: t=-..
2.16 with 32 df, \( p = .038 \)). However, this difference was not significant when baseline scores (\( F = 1.00, p = .32 \)), and premorbid I.Q. (\( F = .96, p = .33 \)) were controlled for. On the Stockings of Cambridge test the fast dopamine D2 dissociating group exhibited shorter composite initial thinking times than the slow dopamine D2 dissociating group (4379 vs. 8239 msec; \( t = -2.31 \) with 18 df, \( p = .032 \)), and they also exhibited shorter initial thinking times for 4 move problems (5083 vs. 8392 msec; \( t = -2.12 \) with 23 df, \( p = .044 \)). When baseline scores were covaried out, the group difference for composite initial thinking times remained (\( F = .048, p = .042 \)), although the group difference for 4 move problems disappeared (\( F = 1.59, p = .21 \)). However, neither difference remained significant when premorbid I.Q. was taken into account (\( p > .45 \) for both measures: see Appendix A.8 iv).

iv) Comparison of clinical symptoms and cognitive performance at 18-month follow-up

For these comparisons there were between 12 and 19 patients in the fast dopamine D2 dissociating group, and between 8 and 11 patients in the slow dopamine D2 dissociating group.

No group differences were observed on clinical measures at 18-month follow-up (\( p > .34 \) for all measures). However, several statistically significant differences in cognitive performance were observed at 18-month follow-up between the fast dissociating group and the slow dissociating group. Firstly, the fast dissociating group achieved a higher score than the slow dissociating group on the Rivermead Behavioural Memory test (19 vs. 15; \( t = 2.71 \) with 24 df, \( p = .012 \)). This difference remained significant after controlling for baseline scores (\( F = 5.99, p = .023 \)), but not after controlling for 9-month follow-up scores (\( F = 2.00, p = .17 \)) or premorbid I.Q. (\( F = .67, p = .41 \)). Secondly, the fast dissociating group scored higher than the slow dissociating group on the pattern recognition test (86 vs. 77%; \( t = 2.06 \) with 23 df, \( p = .050 \)).
Again, this difference remained marginally significant after controlling for baseline scores (F=3.87, p=.062) but not after controlling for scores at 9-month follow-up (F=2.09, p=.16) or premorbid I.Q. (F=.022, P=.88). Thirdly, there was a trend for the fast dissociating group to utilise less initial thinking time than the slow dissociating group, which was statistically significant for 2 move and 4 move problems (Table 5.5). The group difference at the 2 move problem stage remained significant after controlling for baseline scores (F=11.5, p=.003) 9-month scores (F=6.37, p=.019), and premorbid I.Q. (F=5.81, p=.025). This was also the case for the group difference at the 4 move problem stage which remained significant after controlling for baseline scores (F=11.8, p=.002) 9-month scores (F=5.75, p=.026) and premorbid I.Q. (F=10.8, P=.003). In general, there was a trend on the Stockings of Cambridge test for the fast dissociating group to utilise less initial thinking time than the slow dissociating group at all stages (Table 5.5: also see Appendix A.8 v).

**Table 5.5** *At 18-month follow-up the fast dopamine D2 dissociating group used less initial thinking time on the Stockings of Cambridge test than the slow dopamine D2 dissociating group.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (N)</th>
<th>Descriptive statistics (msec)</th>
<th>t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>sd</td>
</tr>
<tr>
<td>Composite initial think times</td>
<td>Fast (15)</td>
<td>4374</td>
<td>1722</td>
</tr>
<tr>
<td></td>
<td>Slow (9)</td>
<td>7366</td>
<td>4486</td>
</tr>
<tr>
<td>Initial think times 2 move problems</td>
<td>Fast (15)</td>
<td>1415</td>
<td>895</td>
</tr>
<tr>
<td></td>
<td>Slow (10)</td>
<td>3371</td>
<td>2446</td>
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<tr>
<td>Initial think times 3 move problems</td>
<td>Fast (15)</td>
<td>3525</td>
<td>1297</td>
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<td>Slow (8)</td>
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<td>1918</td>
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<td>2686</td>
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<td>Slow (9)</td>
<td>13401</td>
<td>7586</td>
</tr>
<tr>
<td>Initial think times 5 move problems</td>
<td>Fast (13)</td>
<td>4969</td>
<td>2244</td>
</tr>
<tr>
<td></td>
<td>Slow (8)</td>
<td>8921</td>
<td>5299</td>
</tr>
</tbody>
</table>
5.8 Individual antipsychotic groups – comparing performance over the study period

i) Baseline comparisons

The key details of the individual antipsychotic groups at baseline are as follows;

- Olanzapine, N=9, mean age =30, mean I.Q. = 91
- Risperidone, N= 9, mean age = 38, mean I.Q. = 94
- Clozapine, N= 11, mean age = 31, mean I.Q. = 107
- Quetiapine, N =8, mean age = 38, mean I.Q. = 98
- Amisulpride, N= 7, mean age = 35, mean I.Q = 97.

No significant differences were found between the individual medication groups in terms of demographic variables (p> .10 for all measures) or clinical variables (p>.43 for all measures). However, a significant cognitive difference was observed between the groups on the graded naming test (F=3.84, with 4, 34 df, p=.011) where the olanzapine group scored less than the other groups (Chart 5.2). In addition, a group difference was found on the ID/ED test in terms of stage reached (F=3.10 with 4,28 df, p=.031) where the quetiapine group completed fewer stages than the other groups (Chart 5.3: see also Appendix A.9 i).
Chart 5.2 At baseline the schizophrenic patients on olanzapine scored less than other groups on the Graded Naming test. (Mean values in boxes)

![Bar chart showing Graded naming test scores for different antipsychotic medications.](chart5.2)

\[ F = 3.84 \text{ with } 4,34 \text{ df, } p = .011 \]

Atypical antipsychotic

Chart 5.3 At baseline the quetiapine group completed fewer stages on the ID/ED test than the other groups (Mean values in boxes)

![Bar chart showing ID/ED stage reached for different antipsychotic medications.](chart5.3)

\[ F = 3.10 \text{ with } 4,28 \text{ df, } p = .031 \]
ii) A comparison of changes in clinical symptoms and cognitive performance over the study period

The number of patients in each antipsychotic group for a particular comparison can be found in appendix A.9. The individual medication groups differed in terms of percentage of maximum dose \((F=3.14, \text{ with } 4, 37 \text{ df, } p=.025)\). Medication dosage per group are displayed in Table 5.6 below.

**Table 5.6 Percentage of maximum dose for individual medications.**

<table>
<thead>
<tr>
<th>Medication group</th>
<th>Mean daily dosage (at 9-month-follow-up)</th>
<th>% of maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>14 mg</td>
<td>70%</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4.8 mg</td>
<td>28%</td>
</tr>
<tr>
<td>Clozapine</td>
<td>430 mg</td>
<td>39%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>375 mg</td>
<td>50%</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>600 mg</td>
<td>51%</td>
</tr>
</tbody>
</table>

No differences were observed between the groups in terms of changes in clinical symptoms between baseline and 9-month follow-up \((p>.16\) for all measures), or between baseline and 18-month-follow-up \((p>.072\) for all measures).

In terms of the cognitive measures, between baseline and 9-month follow-up statistically significant group differences were observed for changes in performance on the spatial recognition test \((F=3.07\) with 4, 27 df, \(p=.033\)), the ID/ED test for stage reached \((F=2.88\) with 4.23 df, \(p=.045\)) and errors at the ED shift \((F=2.66\) with 4, 24 df, \(p=.057\)), and the Stockings of Cambridge test for initial think time for 3 move problems \(F=2.66\) with 4, 24 df, \(p=.057\), and subsequent think times for 4 move problems \(F=3.51\) with 4, 23 df, \(p=.022\).

On the spatial recognition test the group difference can be explained by there being a clear split in terms of changes in performance between medication groups, with the quetiapine and amisulpride groups both improving in performance whereas the other groups showed a decline. (Chart 5.4).
On the spatial recognition test the performance of the quetiapine and amisulpride groups improved between baseline and 9-month follow-up, whereas the performance of the other groups tended to deteriorate (Mean values in boxes).

On the ID/ED test, the group difference in stage reached can be explained by the observation that the clozapine group showed a marked deterioration in performance whilst the amisulpride group showed a marked improvement. In contrast, the performance of the risperidone, olanzapine and quetiapine groups remained unchanged (Chart 5.5). In terms of errors made at the ED shift stage, this difference can be explained by the observation that the clozapine group exhibited an increase in errors whereas the other group all showed a decrease (Chart 5.6).
Chart 5.5 Between baseline and 9-month follow-up the clozapine group deteriorated in terms of stage reached on the ID/ED test, whereas the amisulpride group improved (Mean values in boxes)

\[ F = 2.88 \text{ with } 4, 23 \text{ df, } p = .045 \]

ID/ED stage reached change

![Graph showing ID/ED stage reached change for different antipsychotics.](image)

Atypical antipsychotic

Chart 5.6 The number of ED errors made for the clozapine group increased between baseline and 9-month follow-up, whereas the number of errors made for the other groups tended to decrease (Mean values in boxes)

\[ F = 2.66 \text{ with } 4, 24 \text{ df, } p = .057 \]

Change in errors at ED shift

![Graph showing change in errors at ED shift for different antipsychotics.](image)
On the Stockings of Cambridge test, the group difference for changes in initial think time for 3 move problems is due to the clozapine group showing an increase in latency whereas the other groups all showed a decrease (Chart 5.7). The group difference in terms of changes in subsequent think times at the 4 move problem stage is due there being considerable variability in thinking latency (Chart 5.8: see also Appendix A.9 ii).

*Chart 5.7 Between baseline and 9-month follow-up the clozapine group showed an increase in initial think times whereas the other groups showed a decrease (Mean values in boxes)*
Chart 5.8 The individual medication groups differed in terms of changes in subsequent thinking time for 4 move problems. (Mean values in boxes)

In terms of changes in performance on the cognitive tests between baseline and 18-month follow-up, group differences were only observed on the spatial span test (F=2.95 with 4, 22 df, p=.043), and the Stockings of Cambridge test in terms of initial thinking time for 2 move problems (F=3.10 with 4, 19 df, p=.040) and 3 move problems (F=5.56 with 4, 18 df, p=.004).

On the spatial span test the group difference is due to the olanzapine group showing a large increase in performance whereas the other groups' performances remained relatively constant (Chart 5.9). On the Stockings of Cambridge test group difference for initial think time at the 2 move problem stage can be explained by the observation that the quetiapine group showed a decrease in initial thinking times whereas the other groups showed an increase (Chart 5.10). At the 3 move problem stage the group difference was due to the amisulpride group showing
a large decrease in initial thinking time compared to the other groups (Chart 5.11: see also Appendix A.9 iii).

**Chart 5.9** Between baseline and 18-month follow-up the olanzapine group improved on the spatial span test whilst the other groups showed little change (Mean values in boxes)

![Chart 5.9 showing spatial span test results for different antipsychotics](image)

Atypical antipsychotic

**Chart 5.10** Between baseline and 18-month follow-up the quetiapine showed a decrease in initial thinking time for 2 move problems whereas the other groups showed an increase. (Mean values in boxes)

![Chart 5.10 showing initial thinking time results for different antipsychotics](image)

Atypical Antipsychotic
Chart 5.11 Between baseline and 18-month follow-up the amisulpride group showed a large decrease in initial think time for 3 move problems compared to the other groups (Mean values in boxes).

iii) Comparison of clinical symptoms and cognitive performance at 9-month follow-up

No statistically significant differences were observed between the groups on clinical variables at 9-month follow-up (p>.65). For the cognitive measures, significant group differences were observed on the graded naming test ($F=3.38$ with $4, 32$ df, $p=.020$), where the olanzapine group scored less than the other groups. However, this difference is present at baseline and is reduced to non significance when baseline scores are controlled for ($F=.620, p=.65$).

Several group differences were observed at 9-month follow-up on the Stockings of Cambridge test. Firstly, there was a significant difference in the number of minimum move solutions achieved ($F=6.04$ with $4, 25$ df, $p=.002$). This difference remained significant after baseline scores were controlled for ($F=9.25, p<.0005$) and reflects considerable group
differences in performance (Chart 5.12). Secondly, there was a group difference in composite initial think times (F=4.55 with 4, 27 df, p=.006) which remained significant after controlling for baseline scores (F=3.54, p=.022). This difference reflects the risperidone group exhibiting much longer latencies than the other groups (Chart 5.13). Thirdly, the groups differed for initial think times at the 3 move problems stage (F=3.50 with 4, 31 df, p=.018). Again, this difference was still significant after controlling for baseline scores (F=2.92, p=.039), and again reflected the risperidone group showing the longest latencies (Chart 5.14). Finally, a group difference was observed for initial thinking time at the 4 move problem stage (F=3.49 with 4, 28 df, p=.019). This difference again reflected the risperidone group exhibiting longer latencies than the other groups (Chart 5.15), although this difference was not significant after controlling for baseline scores (F=1.74, p=.17; see Appendix A.9 iv).

Chart 5.12 The risperidone group achieved the highest number of minimum move solutions on the Stockings of Cambridge test, whilst the amisulpride group achieved the lowest. (Mean values in boxes)
Chart 5.13 The risperidone group exhibited longer composite initial think times than the other groups (Mean values in boxes)

Chart 5.14 The risperidone group exhibited the longest initial think times for 3 move problems on the Stockings of Cambridge test (Mean values in boxes)
Chart 5.15 The risperidone group exhibited the longest initial think times for 4 move problems on the Stockings of Cambridge test (Mean values in boxes).

iv) Comparison of clinical symptoms and cognitive performance at 18-month follow-up

No group differences were observed at 18-month follow-up on any clinical measure (p > .63 for all measures). For the cognitive measures, the only statistically significant group differences were found on the Stockings of Cambridge test. Here, the groups differed in terms of composite initial think times ($F=3.71$ with 4, 19 df, $p=.021$) where the olanzapine group exhibited longer latencies than the other groups (Chart 5.16). This difference remained significant after controlling for baseline scores ($F=3.01$, $p=.047$) and was still marginally significant after controlling for scores at 9-month follow-up ($F=2.75$, $p=.060$). The other group difference on the Stockings of Cambridge test was for initial think times at the 4 move problem stage ($F=3.34$ with 4, 19 df, $p=.031$). This was again largely due to the olanzapine group utilising more thinking time than the other groups (Chart 5.17). This difference
remained significant when baseline scores were controlled for (F=3.23, p=.036), but not when 9-month follow-up scores were controlled for (F=1.64, p=.20: see Appendix A.9 v)).

Chart 5.16 At 18-month follow-up the olanzapine group utilise significantly more composite initial think time than the other groups (Mean values in boxes)

![Chart 5.16](image1)

Chart 5.17. At 18-month follow-up the olanzapine group utilised more initial think time for 4 move problems than the other groups (Mean values in boxes).

![Chart 5.17](image2)

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Table 5.7 Shows a summary of the group differences for changes in symptoms and cognition over the study period

<table>
<thead>
<tr>
<th>Group comparison</th>
<th>Changes between baseline and 9-month follow up</th>
<th>Changes between baseline and 18-month follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical antipsychotics vs. atypical antipsychotics</td>
<td>Symptoms No differences. Cognition The atypical group improved on the digit span test whilst the typical group showed no change.</td>
<td>N/A</td>
</tr>
<tr>
<td>1 high 5HT-2A affinity group vs. low 5HT-2A affinity group</td>
<td>Symptoms The high 5HT-2A affinity group showed greater reduction in anxiety / depression than the low 5HT-2A affinity group. Cognition The low 5HT-2A group improved on the digit span and pattern &amp; spatial recognition tests. They also showed a general decrease in thinking times on the Stockings of Cambridge test. The high 5HT-2A group showed no change on the digit span, but worsened on the pattern &amp; spatial recognition tests. They also showed a general increase in thinking times on the Stockings of Cambridge test.</td>
<td>Symptoms No differences. Cognition The low 5HT-2A group improved on the digit span test and showed decreases in thinking time on the Stockings of Cambridge test. The high 5HT-2A group showed no change on the digit span test and increases in thinking times on the Stockings of Cambridge test.</td>
</tr>
<tr>
<td>Multiple receptor blocking group vs. preferential dopamine blocking group</td>
<td>Symptoms No differences. Cognition On the Stockings of Cambridge test the preferential dopamine group showed a decrease in subsequent think time for 2 move problems whilst the multi-receptor group showed an increase.</td>
<td>Symptoms No differences. Cognition The multi-receptor group improved on the Rivermead and spatial span tests. They also showed an increase in thinking time for 5 move problems on the Stockings of Cambridge test. The preferential dopamine group showed a decrement on the Rivermead test and no change on the spatial span test. They also showed a decrease in thinking time for 5 move problems on the Stockings of Cambridge test.</td>
</tr>
<tr>
<td>Fast dopamine D2 dissociating group vs. slow dopamine D2 dissociating group</td>
<td>Symptoms No differences. Cognition The fast dopamine D2 dissociating group showed an improvement on the pattern recognition test, but showed an increase in total errors on the ID/ED test. The slow dopamine D2 dissociating group showed a decrement in performance on the pattern recognition test but showed a decrease in total errors on the ID/ED test</td>
<td>Symptoms The slow dopamine D2 dissociating group showed a greater reduction in withdrawal / retardation than the fast dopamine D2 dissociating group. Cognition On the Stockings of Cambridge test the fast dopamine D2 dissociating group showed a decrease in initial thinking time for 2 move problems whilst the slow D2 dissociating group showed an increase.</td>
</tr>
<tr>
<td>Individual antipsychotic groups</td>
<td>Symptoms No differences. Cognition On the spatial recognition test the quetiapine and amisulpride groups improved whilst other groups showed decrements. For stage reached on the ID/ED test the amisulpride group improved whilst the clozapine group got worse. On the same test the clozapine group showed an increase in ED errors whilst the other groups showed a decrease. On the Stockings of Cambridge test initial think time for 2 move problems increased for the clozapine group whilst it decreased for other groups. For subsequent think time for 4 move problems there was considerable variation between groups.</td>
<td>Symptoms No differences. Cognition On the spatial span test the olanzapine group showed an improvement in performance whilst the performance of the other groups remained constant. On the Stockings of Cambridge test the quetiapine group showed a decrease in initial thinking time for 4 move problems whilst the other groups showed an increase. For initial thinking time for 3 move problems the amisulpride group showed a much larger decrease in thinking times compared to the other groups.</td>
</tr>
</tbody>
</table>
5.9 Considering the effects of co-medication for the 49 patients who continued in the study after baseline

An important consideration for the current study is the prevalence of polypharmacy amongst the patient population. Some medications that are often taken concurrently with antipsychotics can exert cognitive effects, and this factor has the potential to undermine the results obtained. The following section summarises the use of concurrent medications amongst the patient population, and considers whether their prescription would have a confounding effect on the study findings.

j) Antidepressants

A total of 19 patients were prescribed an antidepressant at some stage during their involvement in the study:

*Tricylic antidepressants (2 patients)* – 1 patient was on dothiepin in addition to thioridazine and the other patient was on lofepramine in addition to risperidone. Both patients were on their respective antidepressant for the duration of their involvement in the study.

*Selective Serotonin Re-uptake Inhibitors (SSRIs: 11 patients)* – 5 patients were on paroxetine, and of these, 3 were on risperidone with the remaining 2 on either quetiapine or clozapine. 4 patients were on fluoxetine, 2 of which were on clozapine and the remaining two were on amisulpride or risperidone. 2 patients were on sertraline, with their co-medications being amisulpride and quetiapine respectively. Of the 11 patients on SSRIs, only 4 of these were taking this medication for the whole duration of their involvement in this study.

*Other antidepressants (6 patients)* – All of these patients were on venlafaxine in addition to their antipsychotic. 2 of these were on quetiapine, 2 on risperidone and 2 were either on clozapine or amisulpride. Only 2 of these 6 patients were on an antidepressant for the duration of their involvement in the study.
The patients on an antidepressant were compared to all other patients on all measures at all time points. Two cognitive differences were observed in terms of total change in performance; on the Rivermead Behavioural memory test the group on an antidepressant showed a slight decrement in performance whilst the group on no antidepressant showed a slight improvement (-0.7 vs. +2.9: \( t = -2.55 \) with 25 df, \( p = .017 \)). On the spatial span test the group on antidepressants showed no change whilst the group on no antidepressant showed a slight improvement (0.0 vs. +1.0: \( t = -2.38 \) with 26 df, \( p = .025 \)).

However, it is not thought that being on an antidepressant would have biased the results of this study as use of these drugs was comparable across treatment groups, and most patients were on an antidepressant for only a short period during their involvement in the study. It is therefore assumed that there were no significant confounding effects of antidepressant medication.

Interestingly, there were no differences in ratings of depression or withdrawal/retardation between the patients who were on an antidepressant and those who were not (\( p > .098 \) for all comparisons). This raises questions about the usefulness of using an antidepressant in patients with schizophrenia.

Previous research which has investigated the influence of antidepressants on cognition has found that neither venlafaxine (Nathan et al. 2000) nor sertraline (Hindmarch et al. 1990) have any effect. On the other hand, paroxetine, fluoxetine and the tricylic antidepressants have been reported to have a positive effect on cognition (Cassano et al. 2002: Allain et al. 1992). One tricyclic antidepressant (amitriptyline), has been found to impair memory in one study (Spring et al. 1992). However, all of these studies have been conducted over the short term and the findings are therefore not comparable to the current investigation.
ii) Procyclidine

11 patients were on procyclidine at some stage during their involvement in the study. These patients were distributed equally throughout the individual antipsychotic groups: 3 were on typical antipsychotics, 2 on quetiapine, 2 on risperidone, 2 on clozapine, 1 on olanzapine and 1 on amisulpride. Only 1 patient was on procyclidine for the duration of the study, with the rest stopping this medication after either baseline assessment or 9-month-follow-up assessment.

When comparisons were made between patients on procyclidine and those who were not, four statistically significant differences emerged. For symptoms, those on procyclidine exhibited less withdrawal / retardation at 9-month-follow-up than those not on procyclidine (1.0 vs. 2.7: $t=-2.14$ with 45 df, $p=.037$). In addition, on ratings of thought disorder patients on procyclidine showed an increase between baseline and 18-month-follow-up whereas those who were not on procyclidine showed a decrease (+1.4 vs. -2.3: $t=2.30$ with 29 df $p=.029$). On cognitive measures, patients on procyclidine utilised less subsequent think times for 2 move problems on the Stockings of Cambridge test at 9-month-follow-up compared to those not on procyclidine (22 vs. 818 msec: $t=-2.40$ with 32 df: $p=.022$). Also, in terms of change in performance between baseline and 9-month-follow-up on the Rivermead Behavioural memory test, patients on procyclidine showed a slight decrement in performance whereas those who were not showed a slight improvement (-1.8 vs. +2.0: $t=-2.28$ with 25 df $p=.031$).

Although it is widely recognised that anticholinergic agents such as procyclidine have a negative effect on memory (e.g., Nebes et al. 1997; Spohn & Strauss, 1989; Perlick et al. 1986; Tune et al. 1982), it is unlikely that their use affected the results of the current study for a number of reasons. Firstly, only a small number of patients were on these medications, secondly, these patients were on procyclidine for only a short time during their involvement in the study, and thirdly, these patients were distributed amongst medication groups.
iii) Anxiolytics

9 patients were prescribed an anxiolytic in addition to antipsychotic medication. 5 of these patients were on diazepam in addition to thioridazine (1), flupenthixol (1), quetiapine (1), amisulpride (1) and clozapine (1). 2 of the patients on an anxiolytic were on lorazepam concurrently with depixol and amisulpride respectively. The remaining 2 patients were on clonazepam as well as olanzapine or clozapine. 4 of the patients continued on an anxiolytic throughout their involvement in the study, the other patients discontinued this medication after baseline assessment or 9 month assessment.

When patients on an anxiolytic were compared to those who were not, some differences in symptom measures were observed with the anxiolytic group scoring more than those not on an anxiolytic. However this is to be expected as these patients would have had to have more severe symptoms in order to be prescribed an anxiolytic. On cognitive measures the groups were different in terms of graded naming performance at 9-month-follow-up with the anxiolytic group scoring less than the non anxiolytic group (14 vs. 19: t=-2.26 with 43 df, p=.029). In addition, the anxiolytic group made fewer errors up to ED shift on the ID/ED test at 9-month-follow-up when compared to the non anxiolytic group (6.6 vs. 9.0: t=-2.12 with 38 df, p=.040). No comparisons could be made in terms of changes in cognitive performance over the study period between groups as only 1 of the patients on an anxiolytic completed the study.

Cognitive impairments have been reported for lorazapam (Fluck et al. 1998: Hege et al, 1997: Satzger et al, 1990) and diazepam (Khajuria et al. 1995; Bond & Lader, 1981) in healthy volunteers, and benzodiazepines in general have been reported to impair attentional and memory processes (for a review see Buffett-Jerrott & Stewart, 2002). However, in the current study it is unlikely that being on an anxiolitic would have biased the results due to the fact that few patients were on these medication and those that were, were split between medication groups.
iv) Typical antipsychotics

7 patients were taking a typical antipsychotic concurrently with their study medication. However, in all cases this was short term polypharmacy which only lasted for the crossover period between the finish of one medication and the start of the study medication. 2 patients who were prescribed amisulpride were also prescribed trifluoperazine. Another patient on amisulpride was prescribed chlorpromazine. 2 patients who were on quetiapine were concurrently prescribed thioridazine and trifluoperazine respectively. One patient on olanzapine was also prescribed trifluoperazine. Finally, one patient was prescribed two typical antipsychotics concurrently: thioridazine and flupenthixol. All individual dosages were within therapeutic guideline limits.

When comparisons were made on all variables between the patients who were on two antipsychotics and those on only one, two significant differences were found. On the Rivermead Behavioural Memory test the patients on 1 antipsychotic scored higher than those on 2 antipsychotics at 18-month-follow-up (18 vs. 11: t = -2.73 with 26 df, p = .011). Conversely, on the spatial recognition memory test the patients on 2 antipsychotics scored higher than those on 1 at 9-month follow up (75 vs. 66: t = 3.01 with 22 df, p = .006). There is no research that has explored the effect of more than one antipsychotic on cognition in schizophrenia. However, it is not expected that being on more than antipsychotic would have biased the results in the current study as the number of patients on polypharmacy was small and well distributed amongst the individual medication groups.
v) Hypnotics

A total of 7 patients were taking a hypnotic in addition to the study medication. Of these, 3 patients were on zopiclone in addition to either quetiapine, amisulpride or depixol. 2 patients were on temazepam in addition to risperidone. 1 patient was on nitrazepam in addition to risperidone, and 1 patient was on zolpidem in addition to quetiapine.

In terms of symptoms, the patients on a hypnotic had more symptoms of anxiety and depression than those who were not at both 9-month (8.7 vs. 4.7: t=3.07 with 46 df: p=.004) and 18-month (10.2 vs. 3.0: t=5.10 with 3 df: p=.007) follow-up. This group difference was also reflected in terms of changes in symptoms of anxiety / depression as the decrease in these symptoms between baseline and 18-month-follow-up was significantly smaller for the hypnotic group when compared to the non hypnotic group (-0.75 vs. -3.70: t=2.66 with 29 df: p=.013). A similar pattern emerged with scores on the HDS with the hypnotic group again showing more symptoms at 9-month-follow-up (14.7 vs. 7.1: t=3.64 with 46 df: p=.001) and 18-month-follow-up (13.7 vs. 5.0: t=3.34 with 28 df: p=.002). Also at 18-month-follow-up the hypnotic group scored higher in terms of BPRS total score than the non hypnotic group (18.7 vs. 8.9: t=2.44 with 29 df: p=.021).

On the cognitive measures at 9-month-follow-up the group on hypnotics scored less than the non hypnotic group on the Rivermead behavioural memory test (12 vs. 17: t=2.21 with 42 df: p=.032), and the pattern recognition test (61% vs. 75%: t=2.05 with 44 df: p=.045). The hypnotic group also made more errors than the non hypnotic group on the spatial working memory test at both 9-month-follow-up (64 vs. 38: t=2.77 with 40 df: p=.008) and 18-month-follow-up (61 vs. 35: t=2.06 with 25 df: p=.050).
Studies which have investigated the influence on hypnotics on cognition have yielded conflicting results. Fairweather et al. (1992), Dujardin et al. (1998) and Hindmarch & Fairweather (1994) have reported that zolpidem has no influence on cognition, although some later studies have found a negative influence of this particular hypnotic (Wesensten et al., 1996, Wilkinson, 1995). A similar picture emerges with temazepam with some authors reporting no effect (Wesnes & Warburton, 1984) whilst other report a negative influence but only at high doses (Nakra et al. 1992). For nitrazepam, small negative effects on cognition have been reported (Mattmann et al. 1982). However, all of these studies have involved healthy volunteers and the typical methodology features the volunteer taking the medication one evening, and then being assessed the following morning. No studies have looked at the long term additive effects of these medications, and no studies have explored the effects of these medications in patients with schizophrenia who are on other drugs. Therefore the findings of these studies have little relevance to the present investigation. Indeed, given that the number of patients on a hypnotic was small, and well distributed throughout the treatment groups, it is unlikely that being on this medication would have biased the results.

vi) Mood stabilisers

A total of 6 patients were on a mood stabiliser as well as their antipsychotic medication, 4 of these were on sodium valproate with 1 each on carbamazepine and depakote respectively. Of the 4 patients on sodium valproate, 2 were on olanzapine, 1 was on quetiapine and 1 was on clozapine. The patient on carbemazapine was also on quetiapine and the patient on depakote was also prescribed amisulpride.

When the patients on a mood stabiliser were compared on all measures to those who were not, no clinical differences were observed but there were occasional differences in performance on cognitive tests. Firstly, on the spatial working memory test patients on a mood stabiliser made
fewer errors at 9-month follow-up than those who were not (20 vs. 44: $t=-2.08$ with 40 df, $p=.044$). On the ID/ED test at 18 months the patients on mood stabilisers made fewer errors at the ED shift (5 vs. 16: $t=-3.54$ with 12 df, $p=.004$) and fewer total errors than the rest of the patients (14 vs. 26: $t=-3.77$ with 23 df, $p=.001$). Finally, in terms of minimum move solutions on the Stockings of Cambridge test, the patients on a mood stabiliser displayed a slight decrement in performance between baseline and 18-month-follow-up, whereas the rest of the group showed a slight improvement (-0.66 +1.77: $t=2.23$ with 23 df, $p=.036$).

There is a lack of literature on the cognitive consequences of using sodium valproate, carbamazepine or depakote in schizophrenic patients, although there is a general consensus that anticonvulsants have little effect on cognition (e.g., Kwan & Brodie, 2001). In addition, use of these drugs was comparable across the treatment groups in this study and it is assumed that there were no significant confounding effects.
Chapter 6. Discussion of results over the study period

6.1 Associations between changes in symptoms and changes in cognitive function

Over the 18 months of the study period we found that changes in the symptoms of withdrawal/retardation were negatively associated with changes in thinking times on the Stockings of Cambridge test. As the symptoms of withdrawal/retardation abated there was an increase in thinking time on the Stockings of Cambridge test. Furthermore, BPRS total score and the symptom dimensions of thought disorder and hostility/suspiciousness were also negatively associated with thinking times on the Stockings of Cambridge test. No previous studies have examined the relationship between thinking time on the Stockings of Cambridge test and negative symptoms in schizophrenia.

As the patients who completed the study also showed a significant increase in the number of minimum move solutions between baseline and 18-month-follow-up (6.9 vs. 8.5; \( t = -4.11 \) with 23 df, \( p < 0.0005 \)), it could be suggested that the increase in initial thinking time is associated with an improvement in performance on this test. The patients spend more time thinking about the solution to a problem and are consequently more successful. However, despite the intuitive appeal of this explanation, no correlation was found between changes in minimum move solutions and changes in withdrawal/retardation (\( r = -0.086; n=25; p = .68 \)), which indicates that the increase in initial think time is unrelated to the improvement in minimum move solutions. In addition, despite the improvement in minimum move solutions the patients still performed below that of the control group (8.5 vs. 10.0).

It is generally considered that negative symptoms reflect a failure to engage with or react to stimuli (Mortimer & Spence, 2001), and this conception offers an explanation for poor performance on cognitive tasks which have a timed component. Perhaps the association
between negative symptoms and thinking time reflects the increasing engagement in the task with the reduction in negative symptoms - the patient is more engaged in the task and therefore considers the solution for a longer period.

6.2 Control performance between baseline and 9-month-follow-up

The only improvement for the control group was on the Stockings of Cambridge test where they utilised less thinking time at 9-month-follow-up compared to baseline. This suggests that practice effects are operating with the controls being more familiar with the Stockings of Cambridge test at the second assessment and are therefore quicker to attempt a solution and require less subsequent thinking time. However, this does not result in a change in performance in terms of minimum move solutions with the controls performed near ceiling level on both occasions tested.

6.3 Patients on typical antipsychotics vs. patients on atypical antipsychotics

For clinical variables, no group differences were found either in terms of changes in symptoms between baseline and 9 month follow-up, or at 9-month follow-up. This indicates that both medication classes are equally successful in the remediation of symptoms in schizophrenia. Previous research has indicated that atypical antipsychotics offer no class advantage over typical antipsychotics in terms of negative symptoms (Leucht et al. 1999), although modest advantages have been found in the case of some atypicals. However, in such cases it has remained unclear whether these advantages represent a primary effect, or are merely the consequences of a lack of EPS and the associated motor effects. For positive symptoms, previous research has yielded conflicting findings with some studies finding an advantage of atypicals over typicals (Geddes et al. 2000) whereas other studies have found no clear advantage (Leucht et al. 1999). However, when studies using hundreds of patients have
compared olanzapine and risperidone with typical antipsychotics on measures of positive symptoms, an advantage has been found (Leucht et al. 1999).

In terms of the cognitive data, at 9-month-follow-up the group on atypical antipsychotics reached a higher stage on the ID/ED test than the group on typical antipsychotics. (7.9 vs. 7.0). This indicates that there is a differential effect on attentional set shifting ability between medication groups, with atypical antipsychotics being more beneficial or less detrimental than typical antipsychotics. Indeed, when baseline scores are considered it appears that the typical group have shown a decrement in performance from 8.6 at baseline to 7.0 at 9-month-follow-up, whilst the atypical group have remained constant – achieving stage 8.0 at baseline and 7.9 at 9-month-follow up.

No previous studies have explored the effects of antipsychotic medication on the CANTAB ID/ED test previously. However, one study which investigated the effects of antipsychotic medication on the WCST, a non computerised analogue of the ID/ED test, found that higher doses of typical antipsychotics were associated with increased perseverative errors (Sweeney et al. 1990). These authors suggest that neuroleptic medication has an influence on WCST performance due to its antagonistic effect on the dopaminergic system. This suggestion is consistent with the current findings as the atypical antipsychotics have much lower levels of dopamine receptor occupancy than the typicals (Pillowsky et al. 1992), and therefore would be expected to preserve performance on tests of attentional set shifting. However, in contrast to this study Berman et al. (1986) found that medication free and neuroleptic treated patients did not differ in terms of performance on the WCST, with both groups performing worse than controls. Interestingly, both groups showed a very similar lack of activation of the dorsolateral prefrontal cortex when compared to controls during the WCST. This suggests that neuroleptic medication does not influence performance on the WCST.
The other significant difference at 9-month-follow-up between patients on typical antipsychotics and those on atypical antipsychotics was in terms of minimum move solutions on the Stockings of Cambridge test. Here, the typical group achieved more minimum move solutions than the atypical group. This is a curious finding as no previous studies have found that the typical antipsychotics have a more beneficial influence on cognitive function than the atypical antipsychotics. Certainly there is no neurochemical rationale for such a difference. Perhaps the validity of this finding can be questioned due to the very small numbers in the typical group, and the fact that the p value was only just significant (p=.043) but would be non significant after the Bonferroni correction for multiple testing was applied.

6.4 Patients on high 5HT-2A affinity antipsychotics vs. patients on low 5HT-2A affinity antipsychotics

The rationale for this comparison is based on research which indicates that drugs which antagonise 5HT-2A receptors increase prefrontal dopamine turnover, and this has the potential to improve cognitive function (Friedman et al. 1999a; Meltzer, 1999; Kuroki et al. 1999; Leyson et al. 1998; Lieberman et al. 1998; Hertel et al. 1996; Pehek, 1996 & Schmidt & Fadayal, 1995). In the current study the atypical antipsychotics were categorised in terms of whether they had a high affinity for 5HT-2A receptors (risperidone, olanzapine, clozapine) or a low affinity for these receptors (quetiapine, amisulpride). It might be suggested that the high affinity group would display superior changes in cognitive function to the low affinity group, as the former would trigger a larger increase in prefrontal dopamine turnover than the latter.

Comparing symptoms between groups, the high 5HT-2A affinity group showed a larger reduction in BPRS measures of anxiety / depression than the low 5HT-2A affinity group. This difference was present between baseline and 9-month follow-up, but at no other stage of the
study. As previous research would not suggest differences in symptom response dependent on the 5HT-2A profile of the atypical antipsychotics, there are two possible explanations for this finding. Firstly, it may be a statistical artefact because when the Bonferroni correction for multiple comparisons is applied (multiplying the p value by the number of symptom measures, i.e., 6), the group difference is not statistically significant (p=.10). Another possible explanation for this finding is that although the groups were not statistically different at baseline in terms of anxiety / depression, the high 5HT-2A affinity group did have a higher score compared to the low 5HT-2A affinity group (7.3 vs. 6.0). Therefore there was greater room for improvement for the high 5HT-2A affinity group, which may have resulted in the larger reduction in these symptoms when compared to the low 5HT-2A affinity group.

On the cognitive tests, a number of group differences were found which suggest that low 5HT-2A affinity exerts more beneficial influence on some cognitive processes than high 5HT-2A affinity.

In terms of changes in performance over the study period, the low 5HT-2A affinity group showed an improvement on the digit span test whereas the high 5HT-2A affinity group showed no change. This difference is apparent between both baseline and 9-month follow-up and between baseline and 18-month follow-up. Secondly, between baseline and 9-month follow-up the low 5HT-2A affinity group improve their performance on the pattern and spatial recognition memory tests whereas the high 5HT-2A affinity group show a decrement in performance. Thirdly, there was a general tendency for the low 5HT-2A affinity group to show a decrease in thinking times on the Stockings of Cambridge test, whereas the high 5HT-2A affinity group tended to show an increase in thinking times.

When the groups were compared at 9-month follow up, significant differences were observed in terms of performance on the spatial recognition memory test where the low 5HT-2A
affinity group achieved a higher score than the high 5HT-2A affinity group. In addition, on the Stockings of Cambridge test the low 5HT-2A affinity group tended to utilise less thinking time than the high 5HT-2A affinity group. At 18-month follow up the group difference on the Stockings of Cambridge test remained.

Before discussing these results in terms of their implications for the relationship between serotonergic and cognitive function, it is firstly necessary to consider the reliability of these findings. Indeed, for most of these significant comparisons the P values were between the range of .01 to .05, and are therefore not highly significant. However, these differences show a remarkable degree of consistency, in that they are present at different stages of the test. For the digit span test the group difference was apparent in terms of changes between baseline and 9-month-follow-up, and between baseline and 18-month-follow-up. On the spatial recognition memory test, group differences were observed in terms of changes between baseline and 9-month-follow-up, and when group comparisons were made at 9-month-follow-up. On the Stockings-of-Cambridge test the group differences was evident at all stages of the test. Although the group difference on the pattern recognition memory test was only evident at one stage of the study, it is unlikely that this result is a chance occurrence as this test is very similar to the spatial recognition memory test, and utilises similar cognitive processes. Therefore, despite the p values being rather small, the consistency of these results suggest that they are not chance occurrences or statistical artefacts.

In terms of group comparisons on the digit span and recognition memory tests, the low 5HT-2A affinity group clearly performed better than the high 5HT-2A affinity group. However, on the Stockings of Cambridge test, 'better' performance can not be determined by thinking times alone, rather, it has to be determined by both the number of minimum move solutions and thinking time. As the groups did not differ in terms of minimum move solutions and both performed below that of controls, it cannot be concluded that the low 5HT-2A affinity group performed better than the high 5HT-2A affinity group. However, it can be concluded that the
low 5HT-2A affinity group experienced an increase in their speed of information processing and planning which was not experienced by the high 5HT-2A affinity group. Nevertheless, this increased speed of thought did not confer an advantage in terms of minimum move solutions on the Stockings of Cambridge task. When comparisons are made between the control performance and the performance of both the low 5HT-2A and high 5HT-2A affinity groups, it appears that the low 5HT-2A affinity group more closely resembles the performance of the controls as both groups showed a global decrease in thinking times over the study period. In contrast, the high-5HT-2A affinity group tended to show an increase in thinking times over the study period.

Considering these results in terms of cognitive processes, it appears that atypical antipsychotics which have a low affinity for 5HT-2A (quetiapine and amisulpride) have a beneficial influence on auditory short term memory and recognition memory for patterns and spatial information. In addition, they also decrease thinking time in planning tasks over repeat testing, a characteristic that is similar to the performance of controls. In contrast, the atypical antipsychotics which have a high affinity for 5HT-2A (olanzapine, clozapine, risperidone) have no influence on auditory short term memory, but more importantly they appear to hinder recognition memory for patterns and spatial information. In addition, they also tend to result in an increase in thinking time in planning tasks, a characteristic which does not convey any performance advantage and is the opposite of 'normal' performance in that these patients do not get faster on the task with repeat testing.

It is plausible that there is a common underlying factor which mediates performance on the tests where there is a clear difference between the patients on high 5HT-2A affinity antipsychotics and low 5HT-2A affinity antipsychotics. Indeed, this suggestion has some support as inter-relationships between changes in performance on the digit span, pattern recognition and spatial recognition test were observed in the current study (see Table 6.1).
No significant correlations were found between these measures and most other measures, and so the possibility that these associations are the result of a general change can be discounted.

Table 6.1 Changes in performance on the spatial recognition memory test was associated with changes on the digit span and pattern recognition memory tests

<table>
<thead>
<tr>
<th>Cells contain r (p value) N=26 or 27 for each comparison</th>
<th>Pattern recognition</th>
<th>Spatial recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span</td>
<td>-.015 (.95)</td>
<td>.45 (.020)</td>
</tr>
<tr>
<td>Pattern recognition</td>
<td>.48 (.010)</td>
<td></td>
</tr>
</tbody>
</table>

However, the question remains as to what is the underlying cognitive process which mediates performance on these tests. Clearly the digit span and pattern and spatial recognition memory tests are not similar in terms of the encoding, storing, or retrieving processes involved in information manipulation. Neither are they similar in terms of underlying brain regions responsible for these processes. However, all three tests involve a component of sustained attention as the patients have to attend to the items that are visually or aurally presented to them. If there was an impairment in this process then performance on each of these tests might be compromised.

This suggestion can tentatively be considered to be consistent with the results from the Stockings of Cambridge test where the patients on high 5HT-2A affinity antipsychotics showed an increase in initial thinking time over the study period whilst those on low 5HT-2A affinity antipsychotics showed a decrease. A deficit in sustained attention would augment initial thinking time as the ability to focus on the problem in hand, consider the starting positions of the balls in relation to the target positions, would be impaired. This suggestion has partial support from the current study as positive associations were found between changes in pattern recognition performance and changes in both composite initial thinking time ($r=.37; n=25; p=.70$) and thinking time for 5 move problems ($r=.42; n=24; p=.037$). However, no associations were found between either spatial recognition or digit span and
initial thinking times on the Stockings of Cambridge test. Further empirical investigations are needed to clarify the role of sustained attention in the performance of these tasks, and indeed to explore the association between serotonin, atypical antipsychotics, and this process.

With regard to the previous literature, most of the work which has looked at associations between serotonin and cognition has been done with rats, and the evidence that serotonin plays an important role in learning, memory and attention is now incontrovertible (for a review see Buhot et al. 2000 or Meneses et al. 1999). However, the precise nature of this role in still unclear and appears to be very complex. For example, global manipulation of serotonergic transmission has been shown to exert different effects on cognition from manipulation of the different receptor subtypes. In turn, each receptor subtype is important for different aspects of cognitive function (Buhot et al. 2000). In addition, the anatomical localisation of specific serotonergic receptors has an influence on their cognitive effects. For example, those that are represented in the hippocampal formation, the frontal cortex, the striatum and related structures are considered to be important for memory (Buhot et al. 2000).

To add further complexity to this issue, different types of serotonergic fibres have been identified, those with fine axons and those with beaded axons (Tork, 1990), and some authors have considered that the different types of axons have different influences on cognitive function due to their respective cortical localisation - the fine axons being more densely represented in the frontal cortex whilst beaded axons being more numerous in parietal regions (Mamounas et al. 1991).

Despite these confounding variables, a general theme has emerged over the last ten years which suggests that compounds which increase levels of serotonin result in impairments in tasks which involve learning, memory and attentional processes (Nakamura & Kurasawa, 2000; Meneses, 1998a; 1998b; 1999; Carli & Samanin, 1992). Conversely, depletion of this neurotransmitter exerts the opposite effect, i.e., enhances performance on similar tasks (Meneses et al. 1999; Harrison et al., 1997; Altman et al. 1989; Altman & Normile, 1988).
This pattern of results is true of 5HT-2A receptor subtypes as well as some others, particularly 5HT-1A and 5HT-4 (e.g., Micheau & Van Marrewijk, 1999; Lamirault & Simon, 2001). In addition, a number of studies have found that 5-HT depletion causes an increase in impulsive behaviour in a variety of tasks (Carli & Samanin, 2000; Harrison et al. 1997; Bizot & Thiebot, 1996).

This emerging theme is in direct contrast to the results of the current study where antipsychotics which have a high affinity for 5HT-2A impede some aspects of cognition, and they also lead to increased latency of responding – the opposite of impulsivity – as these patients were slower to begin each solution to the Stockings of Cambridge test. Indeed this group became slower during the testing period whilst both controls and the patients on low 5HT-2A affinity antipsychotics became faster with repeated testing.

Indeed, this discrepancy is especially puzzling as several of the rat studies have utilised a cognitive test which has similarities with some of those used in the current study. In the five choice serial reaction time test of attention food deprived rats are continuously required to detect briefly presented visual stimuli which are presented randomly in one of 5 locations. If the rat responds correctly and within a time limit a food reward is given. This test has been considered to involve sustained attention (e.g., Carli & Samanin, 2000) as the rat has to maintain attentional focus on the area where the light might appear. Therefore this test has similarities, at least at the presentation stage, with the recognition memory tests and digit span test used in the present study.

However, Meneses (1999) suggests that the notion that serotonin activation impairs learning and memory whereas reduced serotonergic function enhances these processes needs reformulating. This is due to number of factors. Some studies have not found the predicted effect; e.g., Jakala et al. (1992) found that depletion of serotonin levels actually impairs performance on an attentional task. Another study has found that antagonism of serotonin
receptors has no influence on rats' performance on attention or memory tasks (Ruotsalainen et al. 2000).

In addition, the cognitive effect of compounds which modify serotonergic transmission depends on whether the compound acts on one receptor subtype or multiple ones, for example, selective 5HT-2A antagonists have been shown to eliminate the positive effects on cognition caused by multiple 5HT receptor agonists, and have also been shown to inhibit the negative effects of others (Meneses, 1999). Also, pre vs. post training administration exerts contradictory effects on performance in some studies (Meneses, 1999).

Of course the generalisation from rats to man can also be questioned, but more importantly, the studies done with rats usually involve compounds which selectively block or destroy specific neurotransmitter systems. In contrast, the atypical antipsychotics act on a number of neurotransmitters simultaneously and therefore they may exert a combined effect on the brain and behaviour which is not seen in more selective compounds. Indeed, the role of serotonergic – cholinergic interactions in the mediation of cognitive behaviour has been considered (Buhot et al. 2000; Steckler & Sahgal, 1995), as have the interactions between noradrenaline, dopamine, serotonin and the cholinergic system (Robbins & Everitt, 1995). In the latter article it is argued that the function of the serotonin system is to dampen the actions of the other systems, which results in behavioural inhibition and cortical de-arousal.

Another important difference between the studies that have been done with rats and the current study relates to the motivation to perform the task successfully. Hungry rats are highly physiologically motivated to perform the task well, whereas human participants may try their best – but they have no physiological imperative to do so. This difference may be reflected in differences in neurotransmitter activity. This is plausible given that serotonin plays a role in
emotional states (Buhot et al. 2000), which would be expected to be different between hungry rats and content humans.

The findings of the current study are also in contrast to those of Chaudhry (2002) who reported that administration of a selective 5HT2 antagonist (cyproheptadine) led to an improvement on several neuropsychological tests in patients with schizophrenia. Patients performed significantly better on the Stroop test, Trails B test and in terms of verbal fluency after 4 weeks of treatment with cyproheptadine. However, no improvements were observed on the WCST or story recall. The authors interpret their findings in terms of the cyproheptadine improving the ability to inhibit responses, but only under condition of time pressure. This is because the patients improved on all tests where response inhibition under time pressure was required in order to perform well. Improvements were not observed on the WCST because although response inhibition was required, this was an untimed task and so according to the authors would not benefit from 5HT2 antagonism. These results are consistent with those of Rosse et al. (1992) who found that reducing levels of serotonin improved performance on the Stroop colour and word tests in patients with schizophrenia. Again, these results might be explained in terms of lowering serotonin levels leading to an improved ability to inhibit responses under time pressure.

Prima facie, it appears that the results of the Chaudhry study are in direct contrast from those of the current study. However, two results are consistent across studies. Firstly, neither study found that 5HT-2A antagonism had an influence on attentional set shifting as measured by the WCST or it’s analogue the ID/ED test. Secondly, if we accept Chaudhry’s explanation that 5HT2 antagonism improves response inhibition when time pressure is placed on a subject, then this could explain why the patients in the high 5HT2 affinity group showed an increase in initial thinking times compared to the low 5HT 2A affinity group. Increased response inhibition meant that the patients considered the solution to the problem for longer periods of
time. Nevertheless, this did not result in any improvement in performance as measured by the number of minimum move solutions.

Further comparisons between the results of the present investigation and those of Chaudhry cannot be made as the cognitive tests used were different. In addition, there are important methodological differences between the two studies which also limit the comparability of findings. Firstly, all the patients in the Chaudhry study were on a typical antipsychotic whereas most in the current study were on an atypical. Secondly, the Chaudhry study only lasted 4 weeks whereas the current investigation lasted for 18 months. Thirdly, only 16 patients were used in the Chaudhry study whereas 49 were used in the current study.

Another study which looked at manipulating serotonin levels and their effects on cognition in patients with schizophrenia was conducted by Soper et al. (1990). They found that reducing serotonin levels through the administration of fenfluramine exerted a negative effect on neuropsychological functioning as measured by a variety of tasks. Indeed, on the digit span test most patients performed worse when taking the study medication, a finding which is partially consistent with the findings of the current study. Furthermore, it can be argued that several of the other tasks in which a decrement was observed involved sustained attention to some degree, e.g., Trails A and B, and therefore the results can again be considered at least partially consistent with those of the current study. However, methodological differences again limit the comparability of findings between Soper et al. (1990) and the current study, for example, they used treatment resistant patients who were taking typical antipsychotics and followed them up over a ten week period.

In healthy volunteers, serotonin depletion has been shown to impair word recognition but only when subjects are tested 30 minutes after taking the serotonin depleting compound (Schmitt et al. 2000). No influence on immediate memory was observed which suggests that memory function is disrupted during the consolidation stage of memory acquisition. When tested later
this deficit remained, but was not augmented. The authors suggest that the timing is important – reducing central 5-HT activity during or immediately after acquisition would disrupt memory function, whereas a reduction of 5-HT activity pre-retention would not. In the same study performance on the Stroop task and a dichotic listening task were both enhanced after reduction of serotonin levels. There was also the suggestion that serotonin reduction caused a degree of impulsivity on the Tower of London test.

In relation to the current investigation these findings are partially consistent. Both studies have found that serotonin reduction impairs recognition memory, however, in the Schmitt et al. (2000) study this was only at a particular time after administration. Unfortunately, in the current study the relationship between the timing of medication administration and cognitive performance could not be determined. It might be expected that the schizophrenic patients had steady levels of serotonin as they were all on regular antipsychotic medication. In terms of the healthy volunteers having an enhanced performance on the dichotic listening task after serotonergic reduction, this finding is in contrast to the suggestion that lowering serotonin levels impedes sustained attention as the dichotic listening task involves this process.

Similarly, serotonergic reduction exerted opposite effects on the Tower of London / Stockings of Cambridge tests between studies, with Schmitt et al (2000) finding an increase in impulsivity whilst the current study found an increase in impulse inhibition. However, one should not expect healthy controls and schizophrenic patients to show the same patterns of performance under different conditions.

Clearly the interaction between serotonin and cognition is a complex one and we are still a long way from elucidating this relationship. Part of this problem lies in the differences between studies, which include; the type of subject (rat, patient, or healthy control); the serotonin altering drug (global manipulation / depletion or specific subtype manipulation / depletion); the timing of drug administration (before, during or after testing); the tests used (which are rarely the same across studies); and the length of the study (short term vs. longer
term). In schizophrenia in particular, there is a strong argument that serotonin research should be prioritised given that most antipsychotic medication has an influence on serotoninergic receptors, and that cognitive impairment is an intrinsic feature of this illness. It is hoped that the results of the current investigation can contribute to this area, and perhaps lead to more extensive work in this field.

6.5 Patients on multiple receptor blocking antipsychotics vs. patients on preferential dopamine blocking antipsychotics

The reason for this comparison is to explore whether the clinical and cognitive effects of the atypical antipsychotics depend on whether they preferentially block one neuro-transmitter system – the dopamine system, or whether they block a number of neurotransmitter systems concurrently. Risperidone and amisulpride belong to the former class, as they exert their influence primarily through the blockade of dopamine receptors. Olanzapine, clozapine and quetiapine, on the other hand, are ‘dirty’ drugs by comparison, as they act on a number of receptors.

No group differences in symptoms were observed either in terms of changes over the study period or when groups were compared at 9-month and 18-month follow-up.

In terms of changes on the cognitive tests, an advantage was observed for the multi-receptor group over the preferential dopamine group on the Rivermead Behavioural Memory test and the spatial span test. On the former, the multi-receptor group improved in performance between baseline and 18-month-follow-up whereas the preferential dopamine group showed a decrement. On the latter, the multi-receptor blocking group also showed an improvement between baseline and 18 month follow-up whereas the preferential dopamine group showed no change. Group differences were also observed at two stages of the Stockings of Cambridge
test, where the preferential dopamine group showed a latency decrease whereas the multi-receptor group showed a latency increase. When the groups were compared at 9-month and 18-month follow up on the cognitive measures, the only difference observed was on the Stockings of Cambridge test at 18-month-follow-up where the preferential dopamine group utilised more initial thinking time for 2 move problems than the multi-receptor blocking group.

One of the main group differences to emerge from this comparison relates to changes in memory function over the study period. On the Rivermead memory test and the spatial span test the multi-receptor blocking group showed an improvement in performance whilst the preferential dopamine blocking group exhibited a decrement in performance on the Rivermead test and no change on the spatial span test.

With regard to the Rivermead test, the group difference can be considered reliable for two main reasons. Firstly, the P value is rather small (P=.010) and the Bonferroni correction is not appropriate in this instance because the Rivermead test is the sole test of long term memory in this study\(^{21}\). Secondly, comparisons between groups at 9-month and 18-month-follow-up are consistent with the findings that the multi-receptor group show greater improvements in long term memory over the study period than the preferential dopamine group. This difference is illustrated in Chart 6.1.

\(^{21}\) To recap, the Bonferroni correction was applied in terms of the number of tests which are purported measure the same ability.
Chart 6.1 The multi receptor group showed superior improvements to the preferential dopamine group on the Rivermead memory test.

However, in terms of the group difference on the spatial span test, these results need to be treated with a degree of caution. This is because firstly, the p value is only marginally significant (p=.042) and becomes non significant when the Bonferroni correction for multiple testing is applied (.042 x 3 = p=.12). Secondly, the group difference does not show a consistent trend over time. Indeed, it is perhaps not surprising that the multi receptor group showed superior changes to the preferential dopamine group on the spatial span test, as they scored lower at baseline and therefore had greater room for improvement.

On the Stockings of Cambridge test, aside from baseline differences, the main group difference was in terms of thinking times where the preferential dopamine group tended to show a decrease over the study period whilst the multi receptor group tended to show a latency increase. As previously noted, controls tend to utilise less thinking time with repeat
testing and therefore the dopamine group show a more normalised pattern of performance than the multi receptor group.

The influence of dopamine on cognitive function is considered to be mediated by several dopaminergic subtypes which are represented in the prefrontal cortex, including D1, D2, D4 and D5 (Knable & Weinberger, 1997). In the current investigation any direct influence of the preferential dopamine blocking antipsychotics (risperidone and amisulpride) on cognition must be via action at the D2 receptor site as these medications have a high binding affinity for these receptors. Conversely, the multiple receptor blocking antipsychotics (olanzapine, clozapine, quetiapine) are devoid of strong affinity for this and other dopamine receptors.

Considering the background literature, there is now indisputable evidence that dopamine manipulation has an influence on working memory (Mehta et al. 2001; Granon et al. 2000; Mehta et al. 1999; Muller et al. 1998; Luciana et al. 1998; Kimberg et al. 1997; Zahrt et al. 1997; Murphy et al. 1996; Arnsten et al. 1995; Sahakian et al. 1985; Brozowski et al. 1979; Goldman et al. 1971). This evidence comes from a variety of sources, including studies involving animals, patients and healthy controls. However, the precise relationship between dopamine and cognition was initially unclear as several animal studies had found that the depletion of cortical dopamine receptors resulted in working memory impairments (Brozowski et al. 1979; Goldman et al. 1971), whereas other studies conversely found that performance on working memory tasks became impaired when cortical dopamine levels were elevated (Zahrt et al. 1997; Murphy et al. 1996; Sahakian et al. 1985). A similarly inconsistent picture emerged with specific regard to the D2 receptor subtype, selective D2 agonists enhance working memory task performance in one study (Arnsten et al. 1995), whilst another study found that D2 antagonism had no effect on working memory task performance (Sawaguchi and Goldman-Rakic, 1991).
The conflicting evidence led Robbins (2000; 1985) to suggest that there is a U shaped relationship between working memory function and dopamine in the prefrontal cortex with extreme high and low levels associated with impaired performance. Presumably any compound which did not modulate levels of dopamine would not have any influence on performance.

Another possible explanation for the conflicting findings is suggested by the results of a study by Granon et al. (2000). Here, dopamine agonism was shown to enhance rats’ performance in the five choice task of attention, but that this was dependent on baseline levels of performance. Rats performing at a comparatively low level experienced an improvement on the dopamine agonist, whilst rats that performed well at baseline showed no change. The opposite effect was observed with a dopamine antagonist – impairing the performance of the high achieving rats but not affecting the performance of the low achieving ones. These results imply that there might be an optimal level of dopamine for a specific given task, and that if the level is too high or too low then performance would be impaired (Robbins, 2000).

Indeed, a series of studies which all used the same compound to deplete dopamine in the marmoset monkey found that such depletion impaired acquisition of the spatial delayed response task (Collins et al, 1998), had no influence on performance on a spatial sequencing task (Collins et al. 1998), but actually facilitated performance on an attentional set shifting test (Roberts et al. 1994). These findings support the suggestion that the nature of the task interacts with dopamine levels to modify performance. In this instance the pattern of performance may suggest that dopamine depletion facilitates distractibility, hence the difficulty with the spatial delayed response task. On the attentional set shifting task the increased distractibility enhances performance because the subject was more aware of seemingly irrelevant stimuli in the test. This latter suggestion might also be sufficient to explain the findings of Granon et al. (2000), who reported that D1 agonists had a beneficial influence on a test of divided attention.
The investigation of the role of dopamine in cognition using healthy human subjects has shown that dopamine agonists can have a beneficial influence on spatial working memory and spatial span (Mehta et al. 2001; Muller et al. 1998; Luciana et al. 1998). Consistent with these studies, the reverse pattern has been observed with dopamine antagonists having been reported to impair spatial working memory, spatial recognition, planning ability and attentional set shifting (Mehta et al. 1999). Although there are inconsistencies in the literature as one study found that recognition memory and planning were unaffected by a D2 agonist (Mehta et al. 2001).

Interestingly, Kimberg et al. (1997) reported that the influence of dopamine agonists' depended on the subject's working memory capacity. High capacity subjects performed more poorly on the drug, low capacity ones improved. These findings are reminiscent of those found in rats in response to a dopamine agonist by Granon et al. (2000).

Further evidence for the importance of dopamine in cognition has been obtained with patient groups. Lange et al. (1992) found that withdrawing L-Dopa from patients with Parkinson's disease resulted in impairments in tests sensitive to frontal lobe dysfunction. There was no decrement on non frontal tests such as recognition memory or visuo-spatial paired associate learning tasks. Another study found that administration of L-dopa led to improvements on tests of executive function over the long term (Growden et al. 1998).

In terms of the current study, our results are not consistent with the background literature. Firstly, manipulation of dopamine has been clearly demonstrated to affect working memory. We found no such effect. This is surprising in the light of the fact that several studies have used the same CANTAB measure of working memory as the current study (Mehta et al. 2001; 1999). One explanation could be that patients were performing so low that dopamine antagonism has no further adverse effect, as was reported in the study by Granon et al.(2000).
Secondly, the studies which have used the CANTAB battery have also found that dopamine manipulation has an influence on tests of spatial recognition, planning ability (Stockings of Cambridge) and attentional set shifting (ID/ED test) (Mehta et al. 2001; 1999). The current study found no such effect.

There are several reasons why the findings of the current study might be inconsistent with previous research.

Firstly, earlier work has either surgically destroyed specific neurotransmitter systems, or utilised compounds which only act on the target neurotransmitter. In contrast, the atypical antipsychotics, even the preferential dopamine blocking ones, have an influence on multiple neurotransmitters. They therefore have the potential to modify cognition through both direct and indirect means.

Secondly, no previous investigations have been conducted with patient groups who have schizophrenia. There are many neuropathological differences between schizophrenic patients, healthy controls and Parkinson's disease patients, particularly with regard to the prefrontal cortex. Therefore the same pattern of response to dopamine antagonism might not be expected. Indeed, when one considers that dopamine depletion is an intrinsic feature of schizophrenia, we should not expect compounds which act on this neurotransmitter to have the same influence on this patient population as either healthy controls or Parkinson's patients. Thirdly, previous studies with humans have been done only over the short term – lasting a maximum of weeks. The current investigation lasted 18 months. It is possible that changes in performance on the working memory tests were observed in the short term, but these effects did not last the whole interval between testing periods. Fourthly, levels of dopamine manipulation from atypical antipsychotics might be different from that of more selective compounds, and therefore might be too small to exert any effect.
On the Stockings of Cambridge test the current investigation found that the preferential dopamine group had a tendency to utilise less thinking time with repeat testing than the multi-receptor blocking group. This might be a practice effect, as seen in the controls, although Jentsch et al. (1997) found that the chemical reduction of dopamine in the prefrontal cortex of monkeys resulted in deficits in response inhibition. These findings are also consistent with those from the current study. However, perhaps more importantly, it is interesting to note that there was a widespread tendency for the multi-receptor group to exhibit longer thinking latencies with repeat testing. This pattern of performance suggests that the multi receptor blocking antipsychotics have a response inhibiting effect, although the neurochemical basis for this result is unclear given the wide ranging influence of these medications.

With regard to our finding that dopamine antagonism impedes long term memory as measured by the Rivermead test, this is the first and only study to report such a finding. Although when one considers the range of memory functions that are utilised during the Rivermead test, it is perhaps not surprising that researchers have avoided this test since simple associations between neurotransmitters or brain regions and specific aspects of memory cannot be obtained. In addition, the strong verbal component of the Rivermead test precludes its use in animal studies. Perhaps a dissection of performance on the Rivermead is needed to look at specific functional impairments, although the individual sub-tests have undergone no reliability or validity investigations independently of the main tests and therefore conclusions from sub-tests scores must be made with caution. It remains to be seen whether the decrement in Rivermead performance is due to a general problem with a specific memory process, such as encoding, storage or retrieval, or whether the deficit is information specific, e.g., involving verbal or non verbal memory.

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22 Indeed, a literature search combining the terms ‘dopamine’ and ‘long term memory’ only yielded 7 hits, none of which were relevant to the current discussion.
6.6 Patients on fast dopamine D2 dissociating antipsychotics vs. patients on slow dopamine D2 dissociating antipsychotics

The rationale for this comparison stems from the work of Kapur and Remington (2001) and Kapur and Seeman (2001) who suggest that antipsychotic atypicality is related to the rate at which individual antipsychotics dissociate from the dopamine D2 receptor. The faster the dopamine D2 dissociation, the more rapidly the drug responds to surges in endogenous dopamine, and the more effective the drug is. This is because transient occupancy does not lead to tolerance or up regulation and makes the system more responsive to antidopaminergic effects. Atypical antipsychotics can be classified in terms of those which have a fast dissociation from the dopamine D2 receptor – quetiapine, clozapine, amisulpride, and those which have a slower dissociation – olanzapine & risperidone.

The only clinical difference between these groups was in terms of changes on the BPRS dimension withdrawal / retardation between baseline and 18-month follow-up. Here, the slow dopamine D2 dissociating group showed a larger decrease in these symptoms than the fast dopamine D2 dissociating group.

On cognitive measures several group differences were observed. Firstly, in terms of changes in performance between baseline and 9-month follow-up the fast dopamine D2 dissociating group showed an improvement on the pattern recognition memory test whereas the slow dopamine D2 dissociating group showed a decrement. Secondly, the fast dopamine D2 dissociating group showed an increase in total errors on the ID/EO test whereas the slow dopamine D2 dissociating group showed a decrease. Between baseline and 18-month-follow-up the fast dopamine D2 dissociating group showed a decrease in initial thinking time for 2 move problems whereas the slow dopamine D2 dissociating group showed an increase.

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When the groups were compared at 9-month follow up the fast dopamine D2 dissociating group had a superior strategy on the spatial working memory test than the slow dopamine D2 dissociating group, although this was not significant when baseline scores were controlled for. In addition, on the Stockings of Cambridge test the fast dopamine D2 dissociating group exhibited shorter initial thinking times at several stages of the test when compared with the slow dopamine D2 dissociating group. At 18-month follow-up the fast dopamine D2 dissociating group performed better than the slow dopamine D2 dissociating group in terms of the Rivermead Behavioural memory test and pattern recognition memory test. A general trend was also observed on the Stockings of Cambridge test with the fast dopamine D2 dissociating group utilising less initial thinking time than the slow dopamine D2 dissociating group.

Despite the large number of differences between the fast and slow D2 dissociation groups, several of these were discounted when premorbid I.Q., baseline performance and corrections for multiple testing were taken into account. Indeed, the differences on the ID/ED test, spatial working memory test and Rivermead test can all be considered unreliable purely on the basis of the group difference in premorbid I.Q.

However, there are several convincing differences between groups. With regard to symptom changes, although the significant difference in withdrawal / retardation is reduced to non significance after controlling for multiple testing (.028 x 6 = .16), the trend over time does suggest that the group difference is reliable. As can be seen in Chart 6.2, the groups have comparable levels of withdrawal / retardation at baseline, but the slow D2 dissociation group exhibits greater reduction in these symptoms over the study period.
Chart 6.2. The slow dopamine D2 dissociation group showed a greater reduction in the symptoms of withdrawal/retardation than the fast dopamine D2 dissociation group.

This difference in symptom change is inconsistent with the suggestion from Kapur and colleagues that faster dissociation has greater efficacy than slow dissociation. Indeed, when one considers the changes in all symptom ratings over the 18 months of the study, the slow D2 dissociation group show superior reductions to the fast D2 dissociation group on all measures except the Hamilton depression scale (see Appendix A.8 iii).

With regard to the group differences on the cognitive tests, the findings from the pattern recognition test and the Stockings of Cambridge test can be considered reliable. On the pattern recognition test the difference was in favour of the fast D2 dissociation group who improved in performance to a greater degree than the slow D2 dissociation group and achieved a considerably higher score at 18-month-follow-up. Controlling for premorbid I.Q. and the Bonferroni correction did not render the p values non significant. Chart 6.3 displays
the group differences on the pattern recognition memory test over time. Interestingly, at 18-month-follow-up the fast D2 dissociation group performed at a level comparable to the control group.

*Chart 6.3* *The fast D2 dissociating group showed greater improvements in performance on the pattern recognition test than the slow D2 dissociating group*

On the Stockings of Cambridge test there was a tendency for the fast D2 dissociating group to utilise less thinking time than the slow D2 dissociating group for both initial and subsequent think times. In addition, the fast D2 dissociating group exhibited a general tendency to use less thinking time with repeat testing, which was not as evident for the slow D2 dissociating group. These differences can be considered reliable as they are consistent throughout the analysis and are largely uninfluenced by premorbid differences in I.Q. However, the groups were comparable at all stages of the test in terms of the number of minimum move solutions.
achieved on the Stockings of Cambridge test. Therefore the group difference in thinking latency does not have an influence on successful task performance.

Unfortunately, no previous investigations of dopamine D2 dissociation speed and cognition have been conducted and therefore comparisons of this study with existing literature can not be made. Although it is known that the D2 receptor does play a role in cognition (e.g., Arnsten et al. 1995), it remains to be seen whether D2 dissociation speed has any direct influence. It is surprising that given the wealth of data suggesting that cognition can be remediated by atypical antipsychotics, none of the published studies on D2 dissociation and antipsychotic medication has considered the potential cognitive effects. Indeed, the originator of this hypothesis, Kapur (2002: personal communication), does not offer any suggestions as to this relationship between D2 dissociation and the cognitive effects of atypical antipsychotics. It is plausible that D2 dissociation speed has no influence on cognition, and that the results of the current study are due to action at other receptors. Indeed, this might be expected since the fast D2 dissociation hypothesis was developed to explain the therapeutic effects of the atypicals, which, as we have seen, are independent from the cognitive effects. Clearly more theoretical and empirical work is needed in this area.

6.7 Individual antipsychotic groups

No group differences were observed on clinical variables in terms of changes over the study period or in terms of comparisons at 9-month or 18-month follow-up. This finding does not suggest that any of the atypical antipsychotics are clinically more efficacious than others. It is important to consider that the patients in the current study were not the most severely ill, and many were living independently or semi-independently. Therefore the results of the current study cannot be used to suggest the equity of treatments for patients with more severe and
enduring aspects of the illness. Nevertheless, our results are consistent with the general background literature.

In a review of the clinical efficacy of clozapine in comparison to olanzapine, risperidone and quetiapine all medications were equally efficacious for positive and negative symptoms (Tuunainen et al. 2002). A trend was reported for clozapine to be more effective than comparators for positive symptoms, but less effective for negative symptoms. This trend was not found in the current study. As a matter of interest, none of the studies featured in the review by Tuunainen et al. (2002) lasted for more than 18 weeks. The current study, with a duration of 18 months, is considerably longer than these and is an important contributor to the literature because it suggests that the individual atypical antipsychotics are equally efficacious over the long term.

Although amisulpride was not included in the review by Tuunainen et al. (2002), it was included in a review by Mota et al. (2002) where it was found to result in more agitation than risperidone, but no other differences in clinical efficacy were found. It appears that on the limited available evidence thus far, the atypical antipsychotics are on the whole equally successful at remediating the main symptoms of schizophrenia. This does not appear to be the case in terms of cognitive function.

One of the main cognitive differences between the individual medication groups was on the spatial recognition memory test. Between baseline and 9-month follow-up the quetiapine and amisulpride groups both improved on this test whilst the olanzapine, risperidone and clozapine groups deteriorated. Although the p value relating to this comparison is not very small (p=.033), this group difference can be considered reliable because it is also present when the groups are compared at 9-month-follow-up. Here, the amisulpride and quetiapine groups achieve a considerably higher score on the spatial recognition memory test than the clozapine and risperidone groups (amisulpride - 81%, quetiapine - 70.6 % vs. clozapine -
65%, risperidone – 61.6%). This difference is approaching significance (P=.085). Therefore the group difference in changes between baseline and 9-month-follow-up is not a chance occurrence, but reflects a consistent group difference. In addition, although the groups are not significantly different in terms of changes in performance between baseline and 9-month-follow-up on the pattern recognition test, the same trend is observed as for the spatial recognition test with both the amisulpride and quetiapine groups showing an improvement (+8.3, +6.2), whilst the olanzapine (-6.2), clozapine (-2.3) and risperidone (-3.6) groups all showed a deterioration in performance. This suggests that visual recognition memory is differentially affected by each individual antipsychotic.

Between baseline and 9-month follow up two group differences were found on the ID/ED test. Firstly, in terms of differences in stage reached the amisulpride group improved in performance and to lesser degree the quetiapine group did also. In contrast, the clozapine group showed a decrement in performance. However, the reliability of this result can be questioned as the p value has only marginal significance and would become non significant after controlling for multiple testing (p = .18). In addition, the group difference is not present at any other stage of the study. Similarly, the group difference in terms of changes in errors made at the ED shift stage of the ID/ED test can also be questioned for much the same reasons – controlling for multiple testing renders the p value non significant (p=.22), and the difference does not show a consistent picture throughout the study. Indeed, stage reached and errors at ED shift on the ID/ED test are inversely related as subjects can not reach later stages on the test unless they make few errors at the ED shift stage.

Between baseline and 18-month-follow-up the group difference on the spatial span test is due to the olanzapine group improving in performance whilst the other groups remained relatively constant. Although the p value relating to this comparison is only marginally significant – (p=.043) and would become non significant with the application of the Bonferroni procedure (p=.12), this result can be considered reliable because it reflects a general trend in changes in
performance over time for the olanzapine group. Between baseline and 9-month-follow-up this group exhibited a greater improvement on the spatial span test than the other groups.

On the Stockings of Cambridge test many group differences were observed at different stages of the study, although several general themes emerged. The risperidone and quetiapine groups achieved more minimum move solutions at 9-month-follow-up than the other groups, and in contrast the amisulpride group performed particularly poorly on this test at this time point. The results can be considered reliable because the p value was highly significant, \( p = .002 \) and unaffected by the Bonferroni correction for multiple testing. However, this group difference was not sustained at 18-month-follow-up.

In terms of thinking times, there was a global trend for the clozapine group to show an increase in both initial and subsequent think times between baseline and 9-month-follow-up and between baseline and 18-month-follow-up. This was not the case for the other antipsychotic groups or controls who had a tendency to show decreases in thinking time with repeat testing. To consider alongside this finding, the clozapine group showed negligible improvement in the number of minimum move solutions over the study period and therefore the increase in thinking latency is not associated with improved planning ability.

The differences in performance between the individual antipsychotics are intriguing and suggest that although some atypical antipsychotics share common neurochemical and cognitive properties, there are also considerable differences between them. The following discussion will focus on the pattern of performance of each individual antipsychotic and consider the neurochemical basis of the cognitive effects observed.
Clozapine exerted a marked detrimental effect on spatial recognition and also had a negative influence on pattern recognition between baseline and 9-month follow-up. Although recognition memory has been rarely investigated in schizophrenia, several studies have also found that clozapine has a detrimental effect on visual memory (Hoff et al. 1996, Goldberg et al. 1993). Another study found that patients treated with clozapine performed worse on tests of visual memory than those treated with risperidone (Daniel, 1994). These results are partially consistent with those from the current investigation. However, one study found that visuospatial memory improved with clozapine (Buchanan et al. 1994).

One possible explanation for the detrimental effect of clozapine on visual memory is related to the anticholinergic properties of this antipsychotic. The anticholinergic system is known to play a vital role in memory (e.g., Drachman & Leavitt, 1974; Coyle et al. 1983), and several authors have reported a relationship between impaired memory and medications which affect the anticholinergic system in patients with schizophrenia (Spohn & Strauss, 1989; Perlick et al. 1986, Tune et al. 1982). Clozapine is considered to be highly anticholinergic when compared to other atypical antipsychotics (Taylor et al. 2001 – Table 6.2), and therefore it is plausible that the visual memory deficits observed are due to the anticholinergic effects of this medication. However, the impairment on tests of visual recognition memory might not be related to memory as such. Meader et al. (1993), reported that the anticholinergic scopolamine disrupts some aspects of visuospatial memory, but suggested that the deficit was one of focussed attention rather than memory, with subjects being unable to successfully attend to stimuli during the presentation stage of a task. This might explain why the clozapine group in the current study did not show a decrement in performance on the Rivermead memory test which would be expected if clozapine causes a memory impairment per se.
Table 6.2. Summary of the side effects of atypical antipsychotics which relate to cognitive performance (adapted from Taylor et al. 2001)

<table>
<thead>
<tr>
<th></th>
<th>Sedation</th>
<th>Anticholinergic effects (memory disruption)</th>
</tr>
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<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Amisulpride</td>
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<td>-</td>
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</table>

+++ High incidence / severity  +++ Moderate incidence  + Low  - Very low

With regard to the observation that the clozapine group used more thinking time, and became slower, on the Stockings of Cambridge test than the other groups, perhaps this is related to the sedative effects of this antipsychotic which have been reported to higher than other atypical antipsychotics (Taylor et al. 2001 – Table 6.2). Indeed, Bender et al. (2001) found that clozapine patients increased their reaction time to the Stroop test between baseline and 4 weeks of treatment, a finding which is partially consistent with the current study.

However, some studies have not demonstrated a cognitive slowing effect of clozapine. Hoff et al. (1996) found that patients on clozapine showed a decrease in mental processing speed after 12 weeks of treatment. In addition, Gallhofer et al. (1999) compared the performance of patients on clozapine with those on risperidone on a maze task. The clozapine group were faster than the risperidone group, but made more errors suggesting a speed vs. accuracy trade off. The authors explained this finding as being due to clozapine having a detrimental effect on the simultaneous processing of cortical and subcortical components of the task, perhaps due to either the anticholinergic or sedative properties of the medication. Indeed, sedation may also be the cause of the visual memory deficits observed in the current study. King (1990) suggests that medications with sedative properties impair sustained attention. It has previously been argued that sustained attention is an important component of recognition memory tasks, and therefore it is plausible that the sedative effects of clozapine might be to
blame for both the visual memory deficits and cognitive slowing apparent in the clozapine group.

Another important question is whether the clozapine dosage might have a negative influence on task performance. However this is unlikely as previous investigations have not found any association between blood levels of clozapine and neurocognitive performance (e.g., Bilder et al. 2002). In addition, compared to the other atypical antipsychotics the dosage of clozapine (expressed as a percentage of maximum dose) is relatively low.

Considering the literature that has compared clozapine with other atypical antipsychotics on tests of cognition, Bilder et al. (2002) explored the effects of clozapine, olanzapine and risperidone using a wide range of neurocognitive tests (although they omitted tests of recognition memory). Clozapine had little positive effect, except on motor performance. In contrast, both risperidone and olanzapine enhanced a wide range of cognitive abilities. Interestingly, on measures of declarative learning and memory the clozapine group showed a slight decrement in performance. Lindenmayer et al. (1998) also found decrements in performance for a group of patients on clozapine, this time the decrements were on tests of executive function and attention. Hoff et al. (1996) also found that clozapine impaired performance on an executive function test. Nevertheless, some evidence does there are beneficial effects of clozapine when compared to other atypical antipsychotics. Lindenmayer et al. (1998) found that their clozapine group showed a greater improvement than the risperidone group in verbal recall and executive function. In addition, Daniel (1994) found that clozapine was more beneficial for tests of vigilance and reaction time than risperidone, although risperidone was more beneficial for tests of set shifting and visual memory.

The results of the current study and those from previous research suggest that clozapine has negligible positive influence on cognitive function, and even exerts negative effects on some aspects of cognition, particularly visual memory. This is in contrast to early reports which
suggested that clozapine can enhance a wide range of cognitive abilities (e.g., Sharma & Mockler, 1998). The reason for the discrepancy between early and late studies is probably to do with the comparator antipsychotics. Most early studies of clozapine used typical antipsychotics as comparators, and given their side effect profile and inferior efficacy will have less beneficial effects compared to clozapine. In addition, many early studies of the cognitive effects of atypical antipsychotics have been methodologically flawed (Keefe et al. 1999) which is probably not the case with more recent research.

Amisulpride

Amisulpride exerted the most beneficial effects on spatial recognition memory in the current study. This might be related to the relative lack of anticholinergic activity of this medication compared to other antipsychotics, or related the fact that it does not exert a sedative effect (Taylor et al. 2001 – Table 6.2). Some reports even suggest that amisulpride may increase alertness (Patat et al. 1999; Grunberger et al. 1989).

However, in contrast to the good performance on tests of visual recognition memory for patients on amisulpride, this group did not perform particularly well on the Stockings of Cambridge test. Here, they achieved the fewest minimum move solutions at 9-month-follow-up and also tended to utilise the least initial and subsequent think time at this time point. This might suggest an association between amisulpride and impulsivity, and might be considered consistent with the reports from healthy controls that amisulpride exerts an alerting effect (Patat et al. 1999; Grunberger et al. 1989) – patients being so alert that they rush into solving the problem rather than thinking about each solution carefully. However, the amisulpride group did not achieve the fewest minimum move solutions or utilise the least amount of thinking time at 18-month-follow-up.
Another plausible explanation for the poor performance of the amisulpride group on the Stockings of Cambridge test relates to the relative lack of affinity of amisulpride for dopamine receptors in the prefrontal cortex (Sanofi, 2000). Amisulpride exerts less influence on prefrontal dopamine than other atypicals, binding preferentially to D2 and D3 receptors in limbic and hippocampal structures (Mattila, 1996). The consequences of this might be to have little or no positive effect on tests which are mediated by the prefrontal cortex, such as the Stockings of Cambridge test. Indeed, between baseline and 9-month-follow-up the amisulpride group were the only ones to show a decrease in minimum move solutions.

In addition, it is plausible that the poor performance of the amisulpride group on the Stockings of Cambridge test relates to dosage. Peretti et al. (1997) found that healthy volunteers taking 50 mg of amisulpride showed a slight decrement in cognitive speed during the Tower of London task 2-3 days after the dose. Interestingly, participants taking 100 mg did not show any adverse effects. Conversely, a study by Ramaekers et al. (1999) found that 400 mg amisulpride had a detrimental effect on semantic reasoning, divided and sustained attention 5 days after administration. This study also used healthy volunteers. However, Perault et al. (1996) found that neither 50 or 200 mg of amisulpride had an effect on cognitive function in healthy volunteers, and Patat et al. (1999) found that 50 mg of amisulpride administered each day over a 4 day period had no negative cognitive or psychomotor effects, and even increased alertness. The mean dose of amisulpride used in the current study was 600 mg (51% of maximum dose), which is much greater than the dose usually given in healthy volunteer studies. Given the previous research it is plausible that this dose of amisulpride could affect performance. However, no previous studies have looked at association between dosage and performance in patient populations with this antipsychotic, or considered the long term effects of taking amisulpride. Therefore at this stage it can not be determined if the dose of amisulpride had an adverse effect on performance on the Stockings of Cambridge test. One study did, however, find that schizophrenic patient’s performance on an attentional task did improve on amisulpride (50 mg/day) compared to placebo (Palliere-
Martinot et al. 1995). As amisulpride is a comparatively new medication, no previous studies have compared its effect on cognition with other atypical antipsychotics.

Quetiapine

Quetiapine exerted similar effects on spatial recognition memory to amisulpride, improving performance between baseline and 9-month follow-up. In addition, the quetiapine group also showed positive changes on the Stockings of Cambridge test. They showed a general decrease in thinking latency over the study period, but more importantly they achieved the second highest number of minimum move solutions at 9-month follow-up, and showed the largest improvement in minimum move solutions between baseline and 9-month follow-up. This pattern of performance – improvement in minimum move solutions combined with decrease in thinking times - is reminiscent of the performance of the control group.

The improvement of the quetiapine group on the spatial recognition memory test and Stockings of Cambridge test might be due to the low sedative and anticholinergic effects of this medication (Taylor et al. 2001 – Table 6.2), although there are other possible explanations.

It has previously been argued that performance on recognition memory tests requires sustained attention. If this ability is impaired than patients will be inefficient at encoding stimuli during the presentation stage of the test and subsequent recognition will be affected. Sax et al. (1998) administered the Continuous Performance test, a test of sustained attention, to a group of schizophrenic patients who were newly prescribed quetiapine. The patients improved in performance on this test over a 40 day period and at final testing achieved scores comparable to those of controls. Therefore quetiapine has been shown to improve sustained attention, and this might explain the improvements on the spatial recognition memory test, and perhaps the improvement observed on the Stockings of Cambridge test. Other studies of
the cognitive effects of quetiapine have also demonstrated improvements on the continuous performance test (Kopala et al. 2001; Meltzer & Lee, 2001). Other aspects of cognition that have been reported to be remediated by quetiapine include domains of verbal fluency and verbal memory (Velligan et al. 2001; Kopala et al. 2001; Meltzer & Lee 2001) as well as executive function (Kopala et al. 2001). In contrast no improvements have been found on the WCST (Velligan et al. 2001; Kopala et al. 2001; Meltzer & Lee 2001), the Stroop test (Velligan et al. 2001), or on visual memory tests (Kopala et al. 2001; Meltzer & Lee, 2001).

However, the neurocognitive changes were not all positive for the quetiapine group. A small decrement in spatial span performance was found between baseline and 18-month follow-up. No other studies have reported this finding, indeed no previous studies have reported that quetiapine has an adverse effect on any aspect of cognition. It is unlikely that the decrement in performance of the quetiapine group on spatial span is due to the dosage used in the current study as this is relatively low (50% of maximum dose) and previous investigations have not found any association between quetiapine dosage and neurocognitive change in schizophrenia (Sax et al. 1998)

Unfortunately no previous studies have compared the neurocognitive effects of quetiapine with those of other atypical antipsychotics and therefore the findings from the current study cannot be compared with the wider literature. Indeed most of the referenced studies of quetiapine and cognition are conference abstracts, which may be methodologically limited. It is likely however, that with the increased routine use of quetiapine more information about its cognitive effects can be obtained.

Risperidone

The patients on risperidone showed several decrements in performance over the study period. Between baseline and 9-month follow-up this group displayed a decrease in performance on
both the spatial recognition memory test and pattern recognition memory test. In addition, this
group showed a slight decrement in performance on the spatial span test between baseline and
18-month follow-up.

However, on the Stockings of Cambridge test the risperidone group achieved the highest
number of minimum move solutions at 9-month-follow-up. They showed reasonable
improvements on this aspect of the Stockings of Cambridge test throughout the study period.
In terms of thinking times, the tendency of this group was to show an increase in initial
thinking time, but a decrease in subsequent thinking time over the study period. Thus
although performing well in terms of minimum move solutions, the pattern of thinking times
displayed by this group were dissimilar to the controls, who showed a general decrease in
both initial and subsequent thinking times.

The negative effects of risperidone are not easily explained with reference to the either its
sedative or anticholinergic effects as these are low. Neither can they be explained as being
due to dosage as previous studies have not found any association between blood levels of
risperidone and neurocognitive performance (Bilder et al. 2002).

Previous investigations of the cognitive effects of risperidone have found improvements in
many domains, including working memory (Green et al. 1997; Rossi et al. 1997), selective
attention and alertness (Stip & Lussier, 1996), executive function (Rybakowski & Borkowska,
2002, Chua et al. 2001; Rossi et al. 1996), learning acquisition, recall consistency and
recognition memory (Kern et al. 1999), verbal fluency (Chua et al. 2001), memory
consolidation (Leander & Wolff, 2002), attentional set shifting (Rybakowski & Borkowska,
2002), visual memory (Daniel 1994), declarative learning and memory (Bilder et al. 2002).

Indeed, when compared to other atypical antipsychotics risperidone has been shown to
perform better than olanzapine (Rybakowski & Borkowska, 2002) and clozapine (Bilder et al.
2002; Gallhofer et al. 1999), on multiple aspects of cognition. Although there is evidence to suggest that the positive effects of risperidone are specific to particular domains of cognitive function. Bilder et al. (2002) reported that although risperidone was superior to olanzapine in terms of declarative learning and memory, the reverse was true for processing speed, attention and general executive and perceptual organisation. Similarly, Cuesta et al. (2001) reported that patients receiving olanzapine showed more improvement in the interference task on the Stroop test than patients on risperidone, although risperidone patients improved more than olanzapine patients in the number of categories achieved in the WCST. Also, Daniel (1994) found that although risperidone exerted superior effects to clozapine on tests of attentional set shifting and visual memory, the reverse was true for tests of vigilance and reaction time. Contrary to these reports, Purdon et al. (2000) found that risperidone produced fewer improvements in cognitive function on a range tests when compared to olanzapine, and was also inferior in terms of change in the general cognitive index.

Some studies have not reported any positive effects of risperidone, and some have reported detrimental effects. Hong et al. (2002) completed an 8 week study of first episode patients treated with risperidone and found no change on tests of sustained attention and vigilance to visual stimuli. Although there was a prolongation of reaction time after treatment which is consistent with the increase in initial thinking time found in the current study.

In addition, on a maze task patients on risperidone were slower, yet more accurate than patients on clozapine, suggesting a speed vs. accuracy trade off (Gallhofer et al. 1999). This is consistent with the current study as patients on this medication achieved a high number of minimum move solutions but at the expense of initial thinking time.

One other study of risperidone and cognition found that although risperidone patients showed mild improvements in cognition over 12 weeks, there was also a non significant decrement in tests measuring attention (Lindenmeyer et al. (1998). In the same study the clozapine group
showed a greater improvement in tests of attention and executive function than those on risperidone.

Olanzapine

The patients on olanzapine showed a slight decrement in performance on the spatial recognition memory task between baseline and 9-month-follow-up. This change is unlikely to be due to either the sedative or anticholinergic effects of this antipsychotic since these effects are the same for olanzapine as they are for quetiapine (Taylor et al. 2001- Table 6.2), and the quetiapine group did not show a decrement in performance on this test. Neither can the effects be explained as being due to dosage of olanzapine because although relatively high compared to other atypical antipsychotics (70% of maximum dose), previous investigation has not found any association between the blood levels of olanzapine and neurocognitive performance in patients with schizophrenia (Bilder et al. 2002).

In contrast to the performance of the olanzapine group on the spatial recognition memory test, a marked improvement was observed for this group on the spatial span test between baseline and 18-month-follow-up. This improvement was superior to that observed by all the other groups, some of which even showed a decrement in performance on this test. This improvement is unlikely to be due to the lack of sedative or anticholinergic effects of olanzapine since quetiapine induces similar levels of these effects yet this group experienced a decrement in performance on this test. On the Stockings of Cambridge test the olanzapine group showed larger improvements in minimum move solutions than the other groups, although at 18-month-follow-up this group achieved the fewest number of minimum move solutions for any group except the amisulpride group. In terms of thinking time, there was a general tendency for the patients on olanzapine to show an increase in initial thinking time but a decrease in subsequent thinking time over the study period. Indeed, when the individual
medication groups are compared at 18-month follow-up the olanzapine group exhibited the longest composite initial and subsequent thinking times of all the groups.

Previous investigations of the cognitive effects of olanzapine have revealed positive effects in the domains of psychomotor speed (Bilder et al. 2002; Nowakowska et al. 1999; Bender et al. 2001; Rybakowski & Borkowska, 2002), attention (Bilder et al. 2002; Cuesta et al. 2001; Bender et al. 2001; Rybakowski & Borkowska, 2002), memory (Leander & Wolff, 2002; Cuesta et al. 2001), executive function (Bilder et al. 2002; Bender et al. 2001) and perceptual organisation (Bilder et al. 2002; Cuesta et al. 2001).

When compared with other atypical antipsychotics, olanzapine has been shown to be more beneficial for cognition than clozapine (Bilder et al. 2002; Bender et al. 2001) and risperidone (Purdon et al. 2000). However, one study found that risperidone exerted a wider range of cognitive improvements to olanzapine in a shorter time span (Rybakowski & Borkowska, 2002). Furthermore, there is evidence that the cognitive effects of olanzapine are domain specific and distinguishable from the cognitive effects of other atypical antipsychotics. For example, Bilder et al (2002) found that olanzapine exerted superior effects to risperidone on measures of processing speed, attention, executive skills and perceptual organisation. In contrast, risperidone was superior in terms of declarative learning and memory. Similarly, Cuesta et al. (2001) found an advantage for olanzapine over risperidone on the WCST, whilst the reverse was true in the interference task on the Stroop test.

Considering the findings of the current study in the light of previous research, no earlier studies have found that olanzapine worsens recognition memory or enhances spatial span. Although this is because no previous studies have utilised these particular tests. It is important to note, however, that no previous studies have found that olanzapine has a detrimental effect on any aspect of cognition. With regard to the Stockings of Cambridge test, Bender et al. (2002) did utilise a version of this test (Tower of London) in their study, and although the
olanzapine group did improve on this test over 26 weeks, the report lacks sufficient detail to enable comparisons to be made with the current study.

To summarise the main neurocognitive effects of the individual antipsychotics found in the current study; clozapine impairs visual recognition memory and slows down information processing in planning tasks; amisulpride enhances visual recognition memory but exerts a negative effect on planning ability which may be due to impulsive responding; quetiapine enhances visual recognition memory and planning ability but impairs spatial span; risperidone impairs visual recognition memory and spatial span but enhances planning ability; olanzapine impairs visual recognition memory but enhances spatial span and planning ability.

On the basis of these findings, it should not be taken for granted that atypical antipsychotics have a global and beneficial influence on cognitive function. Atypical antipsychotics do influence cognitive function in patients with schizophrenia, but these effects can be negative as well as positive, although some domains of cognition appear to be unaffected. In addition, for any individual atypical antipsychotic a number of contrasting effects may be observed which depends on the type of test used and the cognitive function measured.
Chapter 7 Methodological considerations

Although the current study has reported some interesting findings in relation to antipsychotic medication and cognition in schizophrenia, these findings need to be considered in the context of the methodological approach used. A number of authors have highlighted numerous methodological flaws which have undermined research in this area (Harvey & Keefe, 2001; Keefe et al. 1999; Bilder et al. 1992), and therefore it is important to consider the current study in the light of these potential pitfalls. Two recent articles have included set of rigorous and comprehensive standards with which to judge studies of cognitive change in schizophrenia (Harvey & Keefe, 2001; Keefe et al. 1999). The current study will be discussed in relation to these standards as a way of assessing the validity of the findings reported.

**Baseline Pharmacological status**

It is suggested in Keefe et al. (1999) that the ideal baseline condition for patients would be medication free, although they recognise that this is not practicable (nor ethical) in all but first episode cases. However, due to the robust findings that conventional antipsychotics do not improve cognitive function in schizophrenia, they consider it acceptable that patients at baseline need not be medication free if their treatment consists of conventional antipsychotics.

Although this standard does not include a direct caution against baseline assessments being performed on patients who were on a particular atypical antipsychotic which is then changed to another atypical antipsychotic (the study medication) prior to inclusion in the study, the inference from Keefe et al. is that this is not ideal. We would concur with their argument in a situation where a patient is stable and has been on a particular atypical antipsychotic for some time prior to a change. However, it should be recognised that sometimes patients do not respond well to a particular atypical antipsychotic and within a short space of time may have
to be switched to another atypical. In this situation we would argue that it is acceptable to take baseline measures on patients who had previously received treatment with an atypical antipsychotic, providing that this treatment was transient and unsuccessful, and therefore unlikely to have had an influence on the patient's cognitive abilities. This was the case in the present study where the patients recruited comprised a mixture of first episode patients, those who were switching from a typical to an atypical, and those who were switching from one atypical to another atypical. However, the latter group were the least represented.

The standards for baseline inclusion also suggest that it is acceptable research practice to include patients receiving regular medication alongside an antipsychotic, although Keefe et al (1999) caution against taking baseline measures on patients who are, at the time of testing, receiving medication that is new or unusual. This practice may result in an inaccurate cognitive profile at baseline, and render measurements of change grossly exaggerated. For example, a patient who receives anxiety relieving benzodiazepines immediately prior to cognitive testing may not perform to the same level as they would if they were benzodiazapine free. In the present study there were few, if any, cases of patients who were beginning an atypical antipsychotic at the same time as another medication. In several cases the consultant stopped concomitant prescribing in order to begin an atypical, or the concurrent medications continued as before, with only a change in the antipsychotic prescription.

Furthermore, Keefe et al (1999) suggest that the baseline assessment should be performed when a patient has been stabilised on medication for between 4 to 6 weeks. This would minimise the problems which can be associated with medication change, such as uncontrolled side effects and acute symptom exacerbation. In the present study patients were recruited within six weeks of starting an atypical antipsychotic, and within this window some patients had their baseline assessment conducted within weeks, or even days of switching medications. However, as an important caveat to this point, if the patient was experiencing uncontrolled
side effects or acute symptom exacerbation then they were not assessed at that time. Instead, attempts to assess the patient were conducted when the patient was stable. Therefore in the current study no patient was assessed at baseline unless they were stable.

Harvey & Keefe (2001) suggest that baseline assessments need to take into account the lingering effects of old medications, particularly those of typical antipsychotics, which can exert residual antidopaminergic effects for up to 6 months (Farde et al. 1992). However, in the current study these residual effects would have minimal influence on the results as the assessment follow-ups extended far beyond the influence of these residual effects.

Multiple study arms with random assignment

Keefe et al (1999) argue that the best design for clinical trials involves the random assignment of patients to different treatments for the purpose of comparing these treatments on a dependent variable. In studies of atypical antipsychotics, a suitable study would compare 2 or more atypical antipsychotics with each other, or compare an atypical (or more than one atypical) with conventional antipsychotic medication.

Although we agree broadly with this standard, we would argue that it is an acceptable practice in some mental health research to assign patients to treatment group based on clinical need rather than on random allocation. This may mean some treatment groups take longer to be filled, but this method is ethically preferable as it would minimise the conflict between research goals and clinical judgement that may occur on occasions. To add to this point, we would also argue that any potential biased allocation to treatment groups can be investigated with a thorough analysis of the demographic, clinical and cognitive data which would be taken at baseline.
Furthermore, it has been noted that patients who participate in a randomised trial are not a random sample of people with a particular illness, rather, they are a highly selected number of willing, able and eligible patients who may not be representative of the patient population as a whole (Swinscow, 1996). In addition, the gradual withdrawal of typical antipsychotics from routine clinical prescribing means that few future studies will use these medications as comparators against the atypical antipsychotics.

*Double-blind condition*

Keefe et al (1999) suggest that double-blind study methodology is important in studies that use subjective evaluations, such as in symptom rating scales, as part of the assessment. This would prevent knowledge of a patient's treatment group having an influence on their rating. It is also suggested that tests which are considered to be objective, such as cognitive tests, may also be susceptible to researcher bias.

These suggestions imply that a researcher has a vested interest in promoting one medication over another. Although this might be possible in studies which are sponsored by a pharmaceutical company, this is not the case in the current study because the main arm of the research was unfunded and none of the researchers had any interest in promoting a particular medication. In addition, the clinical tools used for patient assessment are well validated and standardised precisely to minimise any subjective element which may contaminate the scoring. In terms of the neurocognitive tests, the CANTAB battery is automated in order to remove the subjective element in scoring.

Therefore, although this study was not blinded the likelihood of a subjective element influencing the results is very small. In addition, the current study was conducted on very limited resources which prevented a double blind methodology being employed.
Adequate duration of trial

The latency of symptom response to the initiation of antipsychotic treatment can be variable. Some authors report a quick response (Conley et al. 1997), whereas others note responses lasting over several months (Lieberman et al. 1994; Wilson 1996). Keefe et al. (1999) suggest that studies of cognitive response to antipsychotics should continue within the same time frame as studies of symptom response, ideally extending over the long term. It is suggested that improvements in cognitive function may take some time, particularly if the area of interest is one of the more complex cognitive abilities such as executive function.

However, to be considered alongside this, Keefe et al also suggest that there may be short term cognitive changes associated with the commencement of atypical antipsychotic treatment. Indeed, Bilder et al (1992) report the immediate influence of methylphenidate hydrochloride on oral word production in schizophrenia, which does suggest that studies of cognitive change need to take account of the short term as well as the long term.

Although the longitudinal nature of the current study means that changes which occur over the long term are likely to be detected, the long interval between assessments might mean that shorter term changes are undetected. This is a valid criticism of the methodology used in the current study, but there are several responses to this criticism. Firstly, one of the main reasons why the study of cognition is important in schizophrenia is because this might give an indication of how a patient is able to cope in everyday life. Therefore the changes that are of interest are the longitudinal ones which might have the potential for long term social benefit. Short term changes, by their very nature, are of less interest in this context because any social improvement is also likely to be short term.
Secondly, a major problem with a study which investigates short term changes in addition to long term changes runs the risk of increased practice effects affecting performance (since the subject would be performing the task many times) and increased incidence of drop outs (since subjects do tend to get tired of multiple testing).

*Clinically appropriate dosing strategies*

In comparing two medications, care should be taken that patients in either group are taking appropriate doses of their respective medications. If patients in one group were on doses of an antipsychotic that had a detrimental affect on motor performance, e.g., 40 mg of haloperidol per day, then reliable comparisons could not be made between this group and a group whose treatment all lay within a reasonable dose range. Indeed, risperidone had been reported to cause extra-pyramidal side effects even at doses considered within a reasonable range (6 to 16 mg) when this antipsychotic was first licensed. Subsequently the suggested usual dose range for risperidone has been changed to between 4-6 mg per day.

In the current study all medication dosage was in the usual maintenance range and therefore side effects from high doses would not have been observed. Although it should be mentioned that patients were not assessed for side effects in this project.

*Appropriate content, properties, and number of neurocognitive measures*

This threefold standard refers to the neurocognitive tools used for assessing change. Firstly, in terms of content, they must assess functions that have been widely reported to be impaired in schizophrenia, such as executive function. In addition, Keefe et al suggest that measures which predict functional outcome, such as memory tests, may be of particular interest. We would add to this point that it is also important to include a control test, i.e., a test which is not
predicted to show any change with treatment, in the battery as this would provide the researchers with the opportunity to confirm that any changes observed were not due to general cognitive improvement, but rather to improvements in specific aspects of cognitive function.

Secondly, Keefe et al propose that any tests used in studies assessing cognitive change should possess the following properties; normative data for use as a comparison; test-retest reliability; absence of floor or ceiling effects; and short presentation time. The authors suggest that ceiling effects may be of particular concern because patients who perform optimally on a test have no room for improvement in subsequent sessions.

With reference to these first two points, the current study did indeed utilise a range of tests which are sensitive to the neuropsychological deficits in schizophrenia. In addition, most of the tests used have adequate psychometric properties, except the ID/ED test which has poor test / re-test reliability. However this problem reflects a general inadequacy with this type of strategy driven test – yet non computer analogues of this test – the WCST- are still widely used to examine change in schizophrenia research.

Thirdly, Keefe et al suggest that the patients should be assessed with a variety of neuropsychological tests covering a range of cognitive functions so that the differential response of different aspects of cognitive function to the antipsychotic can be examined. This battery should be short enough so as not to be influenced by decrements in the patient’s motivation or energy.

With regard to the first point, the current study does meet this standard as patients were assessed using a large battery of neuropsychological tests. The second point also does not pose a problem for the current study as assessments were tailored to the individual need of the
patients, being conducted over one, two or three sessions. This depended on the patients' preference or apparent fatigue.

Appropriate sample size

A calculation of the required sample size that is needed for a particular investigation is important because if too few subjects are used then there will be little likelihood in distinguishing genuine improvements from chance variation, and if too many subjects are used there may be a waste of resources and money (Machin et al., 1997). However, sample size calculations cannot be made unless there is a predicted effect size, and an effect size cannot be predicted unless there has been previous work using the same (or very similar) assessment tools. In research which is using novel assessment tools, such as the CANTAB to explore change, then any prediction of effect size would be spurious. In addition, sample size calculations can only be made for one outcome measure and cannot be made in studies which use several outcome measures. Furthermore, the high proportion of dropouts which are often seen in longitudinal studies of psychiatric populations can render initial sample size calculation redundant. Indeed, few studies of cognitive change in schizophrenia include sample size calculations.

Nevertheless, in comparison to much previous work in this area, the current study has used an adequate sample size for most of the group comparisons that were made. Indeed, for all comparisons made at 9-month-follow-up the sample size in the current study (not including controls or patients on typical antipsychotics) was between 35 and 40. This is a larger sample than those used in most of the studies featured in the review by Keefe et al. (1999). However, comparing the individual antipsychotics did render some treatment groups rather small, especially at 18-month-follow-up. Nevertheless, conclusions that were drawn from these
comparisons were only considered in the light of general trends that were observed throughout the study.

*Discrimination between cognitive enhancement and generalised clinical change*

The cognitive impairment in schizophrenia is not completely independent of other aspects of the illness. Negative symptoms have been found to be associated with cognitive deficits (Addington et al. 1991; Davidson et al. 1995), as have movement disorders (Sorokin et al. 1988; Spohn et al. 1988), and medication side effects (Walker and Green 1982; Earle-Boyer et al. 1991). Furthermore, Keefe et al. suggest that transient aspects of the illness, such as extreme positive or disorganised symptoms, may make testing difficult. These factors should be taken into account when testing a patient, with measures of positive & negative symptoms, side effects and movement disorders, being taken concurrently with each cognitive assessment. Associations between changes in scores for cognitive measures can then be examined in the context of other changes, such as negative symptoms, which may occur.

The current study is compliant with this guideline as measures of symptoms were taken concurrently with the assessments of cognitive function, although no assessment was made of motor disorders. However, the lack of assessment of movement disorders is not considered a critical problem as few incidences of these were observed by the research team, which is perhaps not surprising given the lack of side effects associated with atypical antipsychotics.

In summary, the current study is generally consistent with standards of good methodological practice in this type of research. This indicates that the conclusions drawn should be valid and reliable.
However, there are other methodological issues that need to be discussed which were not highlighted by Keefe et al (1999) or Harvey & Keefe (2001).

The first one of these relates to practice effects. Practice effects refer to the improvement of a persons performance due to repeated exposure to an instrument. Some tests are more susceptible to practice effects than others, particularly those tests where speed is one of the outcome measures, where the task is unfamiliar, or on those tasks that have a single, easily conceptualised solution (Lezak, 1995). Measures of learning and memory also show large practice effects. However, practice effects are less likely to be a confounding factor in performance the longer the interval between test and re test (McCaffrey et al. 2000).

In the current study the possibility of practice effects influencing performance was highly unlikely for a number of reasons;

- Patients were administered parallel versions of the tests where available (Rivermead memory test)
- The relatively long interval of 9 months between assessments was felt sufficient to obviate practice effects.
- The inclusion of a control group means that tests which are likely to be susceptible to practice effects can be easily identified. This was the case with the Stockings of Cambridge test where the controls showed significant decreases in thinking time between baseline and 9-month-follow-up. No other tests were found to be susceptible to practice effects by the control group, and therefore by extension would not be liable to these effects in the patient population.

Another important methodological issue relates to the generally poor performance of the patients compared to the controls. How can we be sure that this poor performance is not due to patients being uncooperative or poorly motivated to complete the tasks? (Lezak, 1995). In
the current study poor motivation or lack of co-operation could not explain the patients inferior performance for a number of reasons;

- Patchy performance. It would be expected that patients with poor motivation to undergo testing would perform poorly on all the tests administered. This was not the case as patients performed poorly on some tests but comparatively well on others.
- Patients were observed throughout the testing session and if they showed signs of tiredness or irritation with the test the session was stopped to give the patient a break.
- Patients were informed as to the nature and length of the testing session prior to administering the tests and all consented to the tests without hesitation.
- Patients were under no pressure to complete the tests and were informed that they were free to leave at any time should they wish. Most did not.

For these reasons it is highly unlikely that a lack of motivation or co-operation could account for the patients poor performance in this study.

In addition to the general methodological issues which have been discussed in relation to the current study, a few issues need to be raised in relation to the use of the CANTAB in patient populations.

Firstly, some of the CANTAB tasks are very long and laborious and as a consequence have the potential to adversely affect motivation, particularly if the patient is not performing well. This is a particular issue with the ID/ED test as the test is short if the patient learns the set shifting rule, but quite long if the rule is not learnt. In addition, the use of feedback can be problematic in this test because if the patient does not guess the rule, then they will be repeatedly presented with negative feedback which may in itself have an adverse motivational effect.
Another problem with the ID/ED test is the ambiguity of the instructions. On this test the subject has to learn which one of two shapes presented on the screen simultaneously is correct. When the subject learns this rule by continually making the correct choice over 8 presentations, the computer changes the rule so that the previously incorrect shape becomes the correct one and visa versa. The task becomes more difficult with shapes becoming more complex, and at the final stages of the task the shapes have a line superimposed on them. In this condition the rule changes from being related to the shape, to being related to the line and the subject has to make this attentional shift. However, each of the 2 shapes is randomly presented in one of four boxes which appear in a star configuration on the screen. Once the subject makes a guess the screen clears and 2 more shapes appear in a different location. The location of the shape is actually irrelevant to the task and is only randomised to prevent stuck-in-set responses.

However, because the instructions only mention that there is a rule that the subject has to learn, some subjects mistakenly assume that the rule refers to the positioning of the shapes, i.e., whether they appear in the top, bottom, left, right, location on the screen, rather than the shapes themselves. In several instances subjects have tried to work out a pattern in the positioning of the shapes rather than focussing on the shapes themselves. Indeed, one subject said 'I can't work out whether the rule is to do with the shape or the position of the shape'. In addition, some subjects mistakenly thought that the rule referred to the location and sequence of shape presentations e.g., the correct rule being construed as; 2 shapes in the top box, followed by the shape on the left hand side and then the shape at the base of the screen. These problems affected the performance of some of the control group as well as the patients, and some subjects with high I.Qs performed poorly on this task because they failed to guess the correct rule, although they clearly did not have any attentional problems. This issue is unlikely to confound performance on more traditional measures of set shifting ability such as the WCST because the rule on this test is more clearly related to the stimulus items, rather
than their position. These problems meant that extreme caution had to be employed when interpreting the results of subjects' performance on the ID/ED test.

Other problems with the CANTAB tests, such as the overly long spatial working memory task, are not specific to this battery of tests but reflect generally problems with some measures of neurocognitive functioning.
Chapter 8 Clinical implications and suggestions for future research

8.1 Clinical implications of the current study

The remediation of the positive and negative symptoms of schizophrenia should always remain the main goal of antipsychotic treatment. However, with the increasing emphasis on encouraging patients to live independent and successful lives it is also important to consider the neurocognitive effects of antipsychotic medication. It would be counter productive to successfully treat a patient’s negative symptoms, if the patient suffers the side effects of sedation and memory loss as a consequence of this. Indeed, sedation and memory loss might lead to very similar patterns of social disruption to negative symptoms.

In addition, the negative neurocognitive effects of some antipsychotics need to be considered in terms of the patient’s individual level of functioning. It might not be a good idea to prescribe clozapine to a patient who is at university or is in employment as this might result in difficulties in education or work.

Another implication of the current study is that there may be a need for increased contact between the patient and health care professionals in order to monitor the neurocognitive side effects of antipsychotic medication. Any developing problems could then be identified early and acted upon, perhaps through the use of psychological therapies or cognitive training strategies. Such resources tend to be in scarce supply. Patients and carers should also be given full and clear information about the neurocognitive side effects of medications that are prescribed so that they can make their own decisions as to the suitability of a particular medication in a particular case. Indeed, although the sedative and anticholinergic side effects
of clozapine are well known by clinicians and researchers, few patients or carers are aware of them.

It is hoped that before too long newer antipsychotics will be available which will not have any of the deleterious effects on cognition that are seen with some of the current medications used in clinical practice.

8.2 Suggestions for future research

The current study is one of the longest and most detailed investigations into the neurocognitive deficits in schizophrenia and how these deficits are affected by antipsychotic medication. However, the study needs to be repeated with a larger sample and perhaps with a blinded methodology. In addition, many questions are left unanswered by this project and there are several issues which need to be investigated with future research.

1) A great deal more investigation is needed into the temporal relationship between antipsychotic medication and the neurocognitive deficits in schizophrenia. For medications that have an adverse effect on cognition, is there a progressive deterioration the longer the patient is on the medication? Is there an initial degradation followed by stability, perhaps as the patient habituates to the medication?, Are there fluctuations in the cognitive effects of the atypical antipsychotics – disrupting and enhancing cognition in phases perhaps as a consequence of changes in the levels of endogenous neurotransmitters? Similar questions can be asked for those medications that have a positive influence on cognition, is this influence progressive, permanent, or temporary? In the current investigation these questions are not answered.

2) Another issue is that is unclear from the current study is how the cognitive effects of atypical antipsychotics influence a patients' ability to live a happy, successful and independent life. For example, it might be predicted that the quality of life of patients on
Clozapine is lower than for those on other medications because of the sedative and negative cognitive effects of this medication. However, it is also possible that the cognitive effects of antipsychotic medication are so subtle that they have no influence on a patient’s functioning in a social environment. This issue needs to be investigated, and an important part of such a study would be the patient’s and carer’s experiences of medication effects.

3) A related area of further investigation involves the assessment of cognition in a naturalistic setting. Although the results of the current study are very interesting and suggest that patient’s cognitive responses to atypical antipsychotics are dependent on the individual medication they are prescribed, it remains unclear what the impact of the cognitive changes have on a patient’s everyday life. A study which uses ecologically valid measures of cognitive function would be suitable for this purpose. Indeed, one such measure is the Rivermead Behavioural Memory test which was used in the current study. Results from this test indicate that atypical antipsychotics which have a multiple receptor blocking profile exert a more positive influence on long term memory than antipsychotics which preferentially antagonise dopamine receptors. No other group differences were observed on the Rivermead test. These results suggest that dopamine is an important neurotransmitter for long term memory, whilst serotonin appears important for short term memory and recognition memory. Suggested ecologically valid measures for further research include the Behavioural Assessment of Dysexecutive Syndrome (Wilson et al. 1996), which measures executive skills, and the Everyday Test of Attention (Robertson et al. 1994), which measures attention and working memory.

4) Another interesting avenue of further investigation relates to the pharmacological remediation of the neurocognitive deficits in schizophrenia. Several studies have suggested that pharmacological strategies might be useful in assisting cognitive recovery (Robbins, 2000; Friedman et al. 1999a). However, no authors have suggested ways of repairing the cognitive deficits which are associated with ongoing antipsychotic treatment. Indeed, the addition of another medication to block the cognitive deficits
caused by some antipsychotic medication might lead to other treatment complications, for example by inhibiting the antipsychotic properties of the treatment medication. One way around this problem would be to use psychological treatments and training, which have had some success (Bell et al. 2001; Wykes et al. 1999; Seltzer et al. 1997).

5) Pharmaceutical companies are continually striving to develop more effective antipsychotic medications, and future research needs to assess the cognitive effects of these once they are licensed for clinical use. Zotepine is the most recently developed antipsychotic that is now used in clinical practice. Little is known about its effect on cognition, although one study found that it was at least as effective as clozapine in improving performance on a maze task (Meyer-Lindenberg et al. 1997). Zotepine has similarities to olanzapine, clozapine and quetiapine because it exerts an effect on multiple receptors rather than being selective for dopamine receptors. It causes a high incidence of sedation but has low anticholinergic effects. Future studies need to compare the cognitive effects of zotepine with the other atypical antipsychotics.

6) Granon et al (2000) reported that the cognitive effects of dopamine manipulation in the rat depended on the rat’s baseline performance. Rats who performed poorly at baseline showed an improvement in performance after administration of a dopamine agonist, whilst rats who performed well at baseline showed no change. The converse effect was observed with a dopamine antagonist, this impaired performance of the high achieving rats but left the low achieving rats unaffected. If the results of this study can be generalised to human patients, it suggests that baseline performance might be an important indicator of the cognitive response to antipsychotic medication. However, it is unclear what the mechanism of action for this phenomenon might be, although it could plausibly be related to the levels of endogenous neurotransmitters which interact with drug effects to modulate arousal. This area needs much further investigation.

7) One of the most interesting findings from the current study relates to recognition memory. Patients are impaired on these tests at baseline, and furthermore, antipsychotics which have a low affinity for 5HT-2A receptors remediate this function whilst those which have
a high affinity for 5HT-2A impair it further. No other studies have reported a similar finding. Future work in this area should have two purposes; 1) to clarify the relationship between serotonin and recognition memory, 2) to elucidate the locus of the recognition memory impairment. It was suggested in the current study that the deficit may be caused by an impairment of sustained attention, although other deficits may also be to blame.

8) Does educational attainment play a role in the response of patients to antipsychotic medication? Swanson et al. (1998) found that schizophrenic patients who had spent more than 13 years in education had lower levels of psychiatric symptoms, better quality of life and better performance on neuropsychological measures than patients who had had less than 13 years of education. This suggests that high educational achievement has a preventative effect on psychopathology and neuropsychological deficits in schizophrenia. It would be interesting to investigate whether these protective effects play a role in the clinical and neurocognitive response of patients to antipsychotic medication. The data from the current study could be used to investigate this suggestion.
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Appendix

This section contains full descriptive and inferential statistics which relate to chapter 5 – Results at 9-month and 18-month follow-up.

A.I Comparisons between patients who dropped out of study after baseline assessment and those who continued.

Table A.I.1. There were no demographic, clinical or cognitive differences between patients who dropped out of the study after baseline assessment and those who continued.

<table>
<thead>
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<th>Variable</th>
<th>Group (N)</th>
<th>Descriptive statistics</th>
<th>t-tests</th>
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<td></td>
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Demographic variables
Clinical variables
Cognitive variables
(none CANTAB)
Table A.1.2 There were no CANTAB differences between patients who dropped out of the study after baseline assessment and those who continued.

<table>
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A.2 Comparisons between patients who dropped out of study after 9-month assessment and those who continued.

Table A.2.1: There were no demographic, clinical or cognitive differences between patients who dropped out of the study after 9-month assessment and those who continued.

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<th>t-tests</th>
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Demographic variables

Clinical variables

Cognitive variables

(non CANTAB)
Table A.2.2 There were no CANTAB differences between patients who dropped out of the study after 9-month assessment and those who continued.

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A.3 Associations between symptom change and cognitive change for the patients who completed the study

A.3.1 Correlation matrix showing the relationship between symptom change and cognitive change over the 18 month study period. (N is between 24 & 31 for all measures).

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<th>BPRS W / R</th>
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A.4 Controls – comparison between baseline and 9-month follow-up

Table A.4.1 The controls showed statistically significant decreases in thinking latency on the Stockings of Cambridge test between baseline and 9-month follow-up

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Visual recognition memory

Working memory

Attentional set shifting

ID/ED test

Planning ability

Stockings of Cambridge test

(all thinking times in msec)
A.5 Patients – comparisons between those on typical and atypical antipsychotics

i) Baseline

Table A.5.1 At baseline there were group differences in terms of symptoms of withdrawal / retardation and depression.

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Table A.5.2 At baseline the groups differed in terms of subsequent thinking time on the Stocks of Cambridge test

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ii) A comparison of change between baseline and 9-month follow-up for patients on typical and atypical antipsychotics

Table A.5.3 Between baseline and 9-month-follow-up the group on atypical antipsychotics showed a superior change on the digit span test compared to the typical antipsychotic group.

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Table A.5.3 There were no differences in changes in performance on the CANTAB tests between groups

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- Visual recognition memory
- Working memory
- Attentional set shifting
- ID/ED test
- Planning ability
- Stockings of Cambridge test
- (all thinking times in msec)
iii) Comparisons at 9 month follow up between the schizophrenic group on typical antipsychotics and those on atypical antipsychotics

Table A.5.5 At 9-month-follow-up there were no clinical or cognitive differences between the patients on typical and atypical antipsychotics

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### Table A.5.6 There were statistically significant group differences on the ID/ED test and Stockings of Cambridge test at 9-month-follow-up

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A.6 Patients – comparisons between those on high and low 5HT-2A affinity antipsychotics.

i) Baseline comparisons

Table A.6.1 There were no differences between groups at baseline in terms of demographic, clinical or cognitive variables

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ii) Comparison of change between baseline and 9-month follow-up

Table A.6.3 Between baseline and 9-month follow-up the high 5-HT-2A affinity group experienced a greater reduction in anxiety / depression symptoms, and a greater increase in digit span performance, than the low 5-HT-2A affinity group.

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Table A.6.4 There were group differences between the high and low 5HT-2A affinity group in terms of changes in performance on the visual memory and Stockings of Cambridge tests.

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### Table A.6.5

The low 5HT-2A affinity group improved on the digit span test whilst the high 5HT-2A affinity group showed no change.

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Table A.6.6 The low 5HT-2A affinity group showed a decrease in thinking times on the Stockings of Cambridge test whilst the high 5HT-2A affinity group tended to show an increase.

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iv) Comparison at 9 month follow up

Table A.6.7 The patients grouped according to high vs low 5HT-2 affinity profile did not differ on clinical or cognitive variables at 9-month-follow-up.

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Table A.6.8 At 9-month-follow-up the low 5-HT-2A affinity group did better on the spatial recognition memory test and were faster on the Stockings of Cambridge test than the high 5-HT-2A affinity group.

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v) Comparisons at 18-month follow-up

Table A.6.9 The schizophrenics grouped according to high vs low 5HT-2 affinity profile did not differ on clinical or cognitive variables at 18-month follow-up.

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Clinical variables

Cognitive variables

(non CANTAB)
At 18-month-follow-up the patients on low 5HT-2A affinity antipsychotics utilised less thinking time on the Stockings of Cambridge test than those on high 5HT-2A affinity antipsychotics.

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A.7. Patients – comparisons between those on multi receptor blocking and preferential dopamine blocking antipsychotics.

i) Baseline comparisons

Table A.7.1 The groups differed in performance on the graded naming test at baseline

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Table A.7.2 The preferential dopamine blocking group achieved more minimum move solutions and utilised more thinking time on the Stockings of Cambridge test than the multiple receptor blocking group

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ii) Comparison of change between baseline and 9 month follow up

Table A.7.3 There were no group differences in clinical and cognitive changes between baseline and 9-month follow-up.

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Clinical variables

Cognitive variables (non CANTAB)
Table A.7.4 A group difference was observed in terms of changes in subsequent think times at the 2 move problem stage of the Stockings of Cambridge test

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Visual recognition memory
Working memory
Attentional set shifting
ID/ED test
Planning ability
Stockings of Cambridge test
(all thinking times in msec)
### Comparison of change between baseline and 18 month follow up

**Table A.7.5 Between baseline and 18-month follow-up the multiple receptor blocking group improved on the Rivermead memory test whilst the preferential dopamine blocking group showed a decrement in performance.**

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**Clinical variables**

**Cognitive variables**

(none CANTAB)
Table A.7.6 Between baseline and 18-month follow-up group differences were observed on the spatial span test and Stockings of Cambridge test.

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iv) Comparison at 9 month follow up

Table A.7.7 At 9-month-follow-up there was a marginal difference between groups on the graded naming test

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Clinical variables

Cognitive variables (non CANTAB)
Table A.7.7 At 9-month-follow-up there were no group differences in performance on the CANTAB tests.

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v) Comparison at 18 month follow up

*Table A.7.8* At 18-month-follow-up the preferential dopamine blocking group achieved a higher score than the multiple receptor blocking group on the graded naming test

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Table A.7.9 At 18-month follow-up the multiple receptor blocking group utilised less initial thinking time than the preferential dopamine blocking group at the 2 move problem stage of the Stockings of Cambridge test.

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A.8. Patients – comparisons between those on fast dopamine D2 dissociating antipsychotics and slow D2 dissociating antipsychotics.

i) Baseline comparisons

A.8.1 The patients on fast dissociating antipsychotics had a higher premorbid I.Q. than those on slow dissociating antipsychotics.

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A.8.2 The patients on fast dissociating antipsychotics had a general tendency to utilise less thinking time on the Stockings of Cambridge test than those on slow dissociating antipsychotics.

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Visual recognition memory
Working memory
Attentional set shifting
ID/ED test
Planning ability
Stockings of Cambridge test
(all thinking times in msec)
ii) Comparison of change between baseline and 9-month follow-up

Clinical measures

Table A.8.3 Between baseline and 9-month follow-up changes in symptoms and cognition did not differ between patients on fast dopamine D2-dissociating antipsychotics and those on slow dopamine D2-dissociating antipsychotics.

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Table A.8.4 Between baseline and 9-month-follow-up the fast D2 dissociating group showed an improvement on the pattern recognition test whilst the slow group showed a decrement.

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iii) Comparison of changes between baseline and 18 month follow up

Clinical measures

Table A.8.5 Between baseline and 18-month-follow-up the slow dopamine D2 dissociating group showed a larger decrease in the symptoms of withdrawal / retardation than the fast dopamine D2 dissociating group.

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Table A.8.6 Between baseline and 18 months the fast dopamine D2 dissociating group displayed an increase in initial thinking time for 2 move problems whilst the slow group showed a decrease.

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Visual recognition memory
Working memory
Attentional set shifting
ID/ED test
Planning ability
Stockings of Cambridge test
(all thinking times in msec)
iv) Comparison at 9-month follow-up

Table A.8. The schizophrenics grouped according to D2 dopamine drop off times did not differ on clinical or cognitive variables at 9-month-follow-up.

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Clinical variables

Cognitive variables (non CANTAB)
Table A.8.8 At 9-month-follow-up there were significant differences in performance between the fast dopamine D2 dissociating group and the slow dopamine D2 dissociating group on the Spatial working memory test and Stockings of Cambridge test.

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v) Comparison at 18 month follow up

Table A.8.9 At 18-month-follow-up the fast dopamine D2 dissociating group achieved a higher score on the Rivermead memory test than the slow dopamine D2 dissociating group.

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Clinical variable

Cognitive variables

non CANTAB)
Table A.8.10 At 18-month-follow-up the fast dopamine D2 dissociating group achieved a higher score on the recognition memory tests and also utilised less thinking time on the Stockings of Cambridge than the slow dopamine D2 dissociating group.

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### A.9. Individual antipsychotic groups

#### i) Baseline comparisons

*Table A.9.1 The individual medication groups were equitable at baseline on demographic variables*

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Table A.9.2 There were no clinical differences between groups at baseline

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ii) Comparison of change between baseline and 9-month follow-up

Table A.9.7 Between baseline and 9-month-follow-up the individual medication groups did not differ in terms of changes in symptom variables

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### iii) Comparison of change between baseline and 18-month follow-up

*Table A.9.12 The individual medication groups did not differ in terms of changes in symptoms between baseline and 18-month follow-up.*

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Table A.9.13 Between baseline and 18 month follow up the individual medication groups differed in terms of changes in performance on the spatial span test

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Between baseline and 18-month-follow-up there were no group differences in changes in performance on the ID/ED test.

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iv) **Comparison at 9-month follow-up**

*Table A.9.17 There were no clinical differences between groups at 9-month follow-up*

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Table A.9.19 At 9-month-follow-up the groups showed no differences on the ID/ED test

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At 9-month-follow-up there were significant group differences in terms of minimum move solutions, composite initial think times, and initial think times for 3 and 4 move problems on the Stockings of Cambridge test.

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Table A.9.21 At 9-month-follow-up the individual medication groups did not differ in terms of subsequent think times on the Stockings of Cambridge test.

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v) **Comparison at 18-month follow-up**

Table A.9.22: At 18-month follow-up there were no group differences on clinical variables

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Table A.9.23 At 18-month-follow-up there were no group differences in performance on the cognitive tests

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Table A.9.24 At 18-month-follow-up the individual medication groups did not differ in performance on the ID/ED test.

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Table A.9.25 shows that at 18-month-follow-up there were significant group differences in terms of composite initial think times, and initial think times for 4 move problems on the Stockings of Cambridge test.

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Table A.9.26 At 18-month-follow-up, the individual medication groups did not differ in terms of subsequent think times on the Stockings of Cambridge test.

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<td>Risperidone (5)</td>
<td>1405 (1774)</td>
<td></td>
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<tr>
<td>Clozapine (7)</td>
<td>927 (827)</td>
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<tr>
<td>Quetiapine (4)</td>
<td>948 (314)</td>
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<tr>
<td>Amisulpride (3)</td>
<td>575 (189)</td>
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<td>Subsequent think times 5 move problems</td>
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<tr>
<td>Olanzapine (4)</td>
<td>1844 (2668)</td>
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<td>0.66</td>
<td>4, 19</td>
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<tr>
<td>Risperidone (5)</td>
<td>967 (713)</td>
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<td>Clozapine (8)</td>
<td>1092 (670)</td>
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<tr>
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<td>543 (798)</td>
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</tr>
<tr>
<td>Amisulpride (3)</td>
<td>641 (706)</td>
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