Willed Action and its Impairment in Schizophrenia

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Abstract

Schizophrenia is a disabling psychiatric disorder characterised by positive symptoms (those which the patients experience and are abnormal by their presence such as hallucinations) and negative signs (when the patients lack some element of normal behaviour such as poverty of speech). Frith (1992) suggested that some of the signs and symptoms of schizophrenia reflect a dysfunction of “willed” actions while the processes involved in “stimulus driven” actions remain largely intact. The patients can perform routine acts elicited by environmental stimuli, but have difficulty in producing spontaneous behaviour in the absence of external cues. The aim of this thesis is to examine this hypothesis using a variety of experimental paradigms and procedures to assess willed initiation and preparation as well as willed suppression of action in schizophrenia.

The aim of Study 1 was to assess the initiation and preparation of willed actions in 10 patients with schizophrenia and 13 controls using reaction time (RT) tasks that differ in the degree to which they involve volitionally controlled versus stimulus-driven responses. Subjects performed a visual simple RT (SRT), an uncued four choice reaction time (CRT) and a fully cued 4 choice RT task. For both groups, fully cued CRTs were significantly faster than the uncued CRTs. However, the S1-S2 interval had a differential effect on CRTs in the two groups. For the normals fully cued CRTs and SRTs were equivalent when S1-S2 intervals were 800 ms or longer. A similar pattern of effects was not seen in the patients with schizophrenia, for whom the fully cued CRT were unexpectedly equivalent to SRT for the 200 ms interval and expectedly for the 1600 ms S1-S2 interval, but not the 3200 or 800 ms intervals. Patients with schizophrenia were able to use the advance information inherent in SRT or provided by the precue in fully cued CRT to speed up RT relative to uncued CRT. However, in the
latter task, where the volitional demands of programming are higher since a different response has to be prepared on each trial, patients showed some unusual and inconsistent interval effects suggesting instability of attentional set.

Study 2 examined performance of 11 patients with schizophrenia and 13 normal controls on two motor tasks (placing pegs in a pegboard and repetitive index finger tapping) under unimanual, bimanual and dual task conditions. The patients with schizophrenia placed fewer pegs and had reduced tapping speed in unimanual and bimanual conditions compared to controls. However the decrement in bimanual performance as a percentage of unimanual performance was not significantly different for the patients and controls on either the pegboard or tapping tasks. In contrast under dual task conditions, for the patients peg placement actually improved relative to unimanual pegboard task, whereas tapping performance deteriorated compared to the unimanual tapping, a decrement that was significantly greater for the patients. Thus the improvement in the visually guided pegboard task was at the expense of the repetitive tapping task.

The aim of Study 3 was to examine the above hypothesis by measuring movement related potentials (MRPs) prior to self-initiated and externally-triggered movements in three groups: 6 patients with schizophrenia with high ratings of negative signs, 5 patients with of schizophrenia with high ratings of positive symptoms and 6 normal controls. Subjects lifted their right index finger at an average rate of once every 3 seconds in two conditions, either as self-initiated movements, or as a response to a tone while MRPs were recorded from frontal, fronto-central, central and parietal sites. The patients with schizophrenia and high ratings of negative signs had significantly reduced amplitude of MRPs for the late and peak components and reduced slope of the early and
late MRPs prior to self-initiated movements. These group differences were not found prior to externally-triggered movements. The patients with schizophrenia with higher ratings of positive symptoms did not differ significantly from the normal controls in terms of amplitude or slope of MRPs prior to self-initiated or externally-triggered movements.

Studies 4, 5 and 6 examined willed suppression. Go no-go RT tests have both a relevant stimulus requiring a response and to-be-ignored stimuli requiring the response to be withheld, i.e. response inhibition. The aim of Study 4 was to examine the ability to withhold a response in conditions with increased complexity of decision-making for identifying ‘go’ stimuli in 14 patients with schizophrenia and 12 normal controls. The aim of Study 5 was to examine the ability to withhold a response in conditions with greater dimensional overlap between the non-target no-go and the target go stimuli in 14 patients with schizophrenia and 12 normal controls. The patients were divided into two groups, the ‘high symptom’ group consisted of the 7 patients with ratings of positive symptoms higher than the group median of 9, and the ‘low symptom’ group consisted of the 7 patients with positive symptom ratings below 9. The patients with ‘high symptom’ ratings had slower RTs than the controls which were significant for the SRT conditions of both tasks, and approached significance for the CRT conditions of both tasks. The differences in SRT or CRT between the ‘low symptom’ group and the controls were not statistically significant for either task. In Study 5 the controls showed greater slowing between CRT1 and CRT2 than between CRT2 and CRT3, whereas the RTs of ‘low symptom’ patients did not differ at all between CRT1 and CRT2 and slowed greatly for CRT3. Both patient groups had slower response times than controls in the Hayling test, and produced significantly fewer words in the alternating word
fluency task compared to the controls. Performance on the cognitive tasks correlated with performance on the no-go tasks.

Negative priming refers to the slowing of reaction times that occurs when an ignored distractor stimulus in a first trial (prime) becomes the target stimulus in the subsequent trial (probe) (Tipper, 1985). Unlike normal controls, patients with schizophrenia fail to show significant negative priming, that is, the significant delay of reaction times on probe trials are not present (Beech et al., 1989; David, 1995). The aim of study 6 was to examine the spatial negative priming effect in schizophrenia using a new paradigm that allows the effects of perceptual mismatch on RT to be considered independently of any spatial negative priming effects. The patients with schizophrenia did not show any spatial negative priming in conditions with or without perceptual mismatch. These results constitute the first unequivocal demonstration of impaired inhibitory processes in schizophrenia based on reduced negative priming effects.

These results provide some overall but not uniformly consistent support for the hypothesis that patients with schizophrenia have an impairment in willed action while stimulus driven action remains intact.
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The Extent of My Personal Contribution

In accordance with the requirements of the University of London, the extent of my personal contribution to the work in this thesis is specified as follows:

During part of the time in which the work was carried out, I was employed as a full time researcher on grants from the Brain Research Trust (2 years) and The Wellcome Trust (1 year). The grant holder was Dr M. Jahanshahi, Department of Clinical Neurology, University College London. My primary supervisor for my thesis was Dr Jahanshahi and my secondary supervisor was Professor C. D. Frith. I made a major contribution to the design of the studies contained in this thesis; I collected all the data and completed all the data analysis.

This thesis is entirely my own original work and no other person should be held accountable for its contents.

Rebecca L. M. Fuller

I certify that this is a correct statement of Rebecca L M Fuller’s contribution

Dr M. Jahanshahi

Department of Clinical Neurology
CHAPTER 1

An Introduction to Schizophrenia

1.1 What is Schizophrenia?

1.1.1 Diagnostic Criteria

Schizophrenia is a severely disabling psychiatric disorder characterised by many different symptoms. Kraepelin (1906) first described *dementia praecox*, later to be known as schizophrenia, in terms of a functional psychosis for which there was no known organic cause. He spoke of the gradual development of the illness, and the difficulty of pinpointing its onset. He stated that in most cases, if there is improvement it is only temporary. Bleuler (1911) first used the term ‘schizophrenia’ to refer to the ‘splitting of psychic’ functions. He described schizophrenia as a group of psychoses that vary in severity, are sometimes chronic, and offer little chance of complete recovery. Today there is still no known cause for schizophrenia. It is not characterised by a single symptom, but is diagnosed based on the presence of a series of abnormal symptoms and behaviours persisting for 6 months and overall impairment in social functioning (See Table 1.1).

1.1.2 Epidemiology and Course

The lifetime risk of developing schizophrenia is about 1 in 100 (DSM-IV, 1994) and the age of onset is usually the early to middle twenties for men and the late twenties for women (DSM-IV, 1994). It is equally common in men and women and appears to be unrelated to cultural or social factors (DSM-IV, 1994).
Table 1.1 Diagnostic Criteria for Schizophrenia

A. Characteristic Symptoms: 2 or more of the following *:

1. Delusions
2. Hallucinations
3. Disorganised Speech (e.g., frequent derailment or incoherence)
4. Grossly Disorganised or Catatonic Behaviour
5. Negative Signs i.e. affective flattening, alogia, or avolition

*Only one of these symptoms are required if the delusions are bizarre or hallucinations consist of a voice keeping a running commentary on the person's behaviours or thoughts, or two or more voices conversing with each other.

B. Social/ Occupational Dysfunction: 1 or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to onset.

C. Duration: Continuous signs of the disturbance persist for at least 6 months. The 6-month period must include at least 1 month of symptoms that meet criterion A.

D. Exclusions: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.


The onset and course of schizophrenia is variable. Many individuals either perform below siblings in school, or have trouble in adulthood holding down jobs and are usually employed at a lower level than their parents. This leads to 'downward drift' and as a result, more patients with schizophrenia are reported from the lower levels of the socio-economic strata. Individuals normally go through a prodromal stage marked by
slow development of various signs and symptoms such as social withdrawal, deteriorating hygiene or sudden outbursts of anger. Often family members will refer to the individual as 'going through a phase'. Later the appearance of clear characteristic symptoms such as auditory hallucinations or firmly held delusions lead to the individual seeking/being sent for hospital treatment, at which point schizophrenia is usually diagnosed. The course of schizophrenia varies among individuals. Some report many fluctuations between episodes of severe symptoms and remission while others remain chronically ill. Complete remission is rare. Of those who remain chronically ill, some show a stable course while others worsen progressively.

1.2 Heterogeneity of Schizophrenia

Schizophrenia is universally accepted as a heterogeneous disorder (Andreasen et al., 1999) as patient profiles differ greatly in terms of the neurophysiological dimensions as well as the clinical dimensions of aetiology, treatment response, outcome, cognitive dysfunction and most importantly the diagnosis and symptoms.

1.2.1 Aetiological Heterogeneity

Although, by definition, schizophrenia is diagnosed in the absence of any physical injury to the brain, a substantial amount of research has been conducted to discover the underlying organic nature of schizophrenia.

Twin and adoption studies have shown that an inherited vulnerability to schizophrenia exists (Kendler, 1983; Kety et al., 1968; Kety et al., 1994), but the search for a 'schizophrenia gene' has not refuted the heterogeneity argument. Whereas schizophrenia was found to be linked to chromosome 5 in several British and Icelandic families (Sherrington et al., 1988) there was no link between schizophrenia and that
chromosome in a large Swedish family (Kennedy et al., 1988). A link between schizophrenia and chromosome 22 has been reported by some (Coon et al., 1994; Vallada et al., 1995) but not found by others (Kalsi et al., 1995). While there is a general belief that genetic factors play an important role in schizophrenia, as monozygotic twins have a concordance rate of 48% instead of 100%, it appears that in addition to genetic predisposition some combination of environmental factors also are involved (Wright and Woodruff, 1995).

It is also accepted that a large proportion of patients diagnosed with schizophrenia are sporadic cases as no relatives have suffered from the disorder (Dalen and Hays, 1990). Explanations for the sporadic cases of schizophrenia include obstetric complications during birth or a viral infection during pregnancy. While studies have reported links between obstetric complications and schizophrenia (Dalaman et al., 1999; Eagles et al., 1990; Lane and Albee, 1966; Woerner et al., 1971), most individuals born with obstetric complications do not go on to develop psychiatric disorders (Buka et al., 1993). A study of the Finnish influenza epidemic of 1957 reported increased rates of schizophrenia in people exposed to viral infections during the second trimester of development (Mednick et al., 1988), but this finding was not replicated in a Scottish study of influenza epidemics (Kendall and Kemp, 1989) and subsequently other studies have found no association between schizophrenia and influenza prevalence at any month of prenatal life (Westergaard et al., 1999).

1.2.2 Heterogeneity in Treatment Response and Outcome

Conventional antipsychotics have been administered for more than 40 years to treat schizophrenia, yet there seems to be no standard dosage. Instead a patient's medication is often determined by trial and error, adjusting the dose until symptoms reduce or
extrapyramidal side-effects prevent an increase. The dosage of antipsychotic drugs only weakly predicts their therapeutic effects and there is marked individual variability in the handling of antipsychotics (Davis 1974). Early studies found that approximately 10% of patients are either worse or show no change with antipsychotic treatment and about 20% of patients only improve minimally (Cole et al., 1964; Goldberg 1985). More recent studies have shown that 50 to 75 percent of patients with schizophrenia respond favourably to conventional antipsychotics (Lautin et al., 1980; Mattes et al., 1985; Pickar et al., 1992; Siris et al., 1987) suggesting that 25 to 50 percent of patients with schizophrenia have an unsatisfactory response to conventional antipsychotics.

The new atypical antipsychotics, for example Clozapine, differ from the conventional antipsychotics in that they do not produce standard or 'typical' dopamine receptor blockade effects in animals (Farde et al., 1992; Meltzer et al., 1989). They were designed to produce fewer extrapyramidal side-effects and some studies have reported an improvement in the negative signs (Meltzer et al., 1986, Coryell et al., 1990) but not all have reported this improvement (Johnstone et al., 1979, Angrist et al., 1980).

The outcome of schizophrenia varies greatly across individuals (Davidson and McGlashan 1997). Length of hospitalisation differs, as seen in a longitudinal study where the mean duration of hospitalisation was 13.7 months over a 10-year period with a range of less than one month to 120 months (Johnstone 1992). Long-term outcome differs as well. Generally patients with lower ratings of pre-morbid social relationships and life skills have a greater chance of poor long-term functioning than those with higher pre-morbid ratings (Fenton and McGlashan, 1987), but reports show that some patients fully recover while others remain continuously incapacitated and many lie in between (Riecher-Rossler and Rossler, 1998; McGlashan and Carpenter, 1988; Angst,
1988; Lin and Kleinman, 1988). While it is generally accepted that outcome is poor for patients having a long duration of illness, there are still reports of late onset improvement in patients with schizophrenia (McGlashan 1986).

1.2.3 Cognitive Neuropsychological Heterogeneity

Cognitive impairment in schizophrenia has been reported in thousands of studies since Kraepelin’s and Bleuler’s clinical accounts of schizophrenia in areas including attention, memory and abstract reasoning and problem solving (Gold and Harvey, 1993). While it is widely accepted that patients with schizophrenia have an underlying cognitive deficit, the exact nature of this deficit has not been determined. The heterogeneity of cognitive dysfunction in schizophrenia lies in both the degree of impairment and in performance deficits (Shallice et al., 1991). Although many studies have reported impaired performance of patients with schizophrenia on a particular task, there are always exceptions, for example, performance on the Wisconsin Card Sort Task was impaired in patients with schizophrenia in a study by Weinberger et al. (1986) yet Braff et al. (1991) found no significant differences between patients and controls on this task.

There have been numerous attempts to derive subtypes of schizophrenia based on cognitive function (Goldstein, 1990; Heinrichs and Awad, 1993; Goldstein and Shemanksy, 1995). These authors found widespread cognitive heterogeneity among the patients with schizophrenia, but they discovered four to five groups around which the results cluster. The two extreme clusters include one group with near normal cognitive function and one group with greatly impaired cognitive function while the middle groups were moderately impaired on the cognitive tasks, differing on the amount of
psychomotor impairment (Goldstein, 1990; Heinrichs and Awad, 1993; Goldstein and Shemansky, 1995). Thus within these groups of patients with schizophrenia there were very differing results, from practically normal to severely impaired performance on tasks such as the WSCT, the California Verbal Learning Test, The Purdue Pegboard, Trail Making Test. An attempt to discover significant associations among four similar WAIS-R-based clusters and symptom profiles proved unsuccessful (Seaton et al., 1999). Other studies have failed to find an association between ratings of symptoms and cognitive impairment (Dickerson et al., 1991) although many studies have found that neuropsychological deficits appear to be associated with negative signs (Johnstone et al., 1976, Frith 1992, Braff et al., 1991, Merriam et al., 1990).

Outside influences may add to the heterogeneity of cognitive function in schizophrenia, such as age at testing, length of illness, length of institutionalisation, amount of education, intellectual level, medication level, type of medication (typical vs atypical antipsychotics) comorbidity or neurological complaints but the diversity of cognitive function in schizophrenia is most likely explained by the heterogeneity within schizophrenia itself (Goldstein and Shemansky, 1995).
1.2.4 Heterogeneity of Symptoms

Perhaps the area of greatest heterogeneity in schizophrenia is in the classification and diagnosis of the disorder. While Kraepelin (1906) divided the disorder into four subtypes (catatonic, hebephrenic, paranoid and simple) Bleuler (1911) focused on two types of symptoms, fundamental symptoms (disturbances of associations and changes in emotions) and accessory symptoms (including hallucinations, delusions and abnormal behaviours). Later Schneider (1959) suggested that certain positive symptoms such as commentary hallucinations, thought withdrawal and insertion, which are not seen in other disorders, could be considered the defining characteristics of schizophrenia.

The experiences of patients with schizophrenia vary greatly. Imagine a man who has little facial expression, remains in bed most of the day, fails to even get up to turn on or off the television, responds to questions in single word answers and has no desire to speak or even be close to his family and friends. Now imagine a woman who is convinced that someone is bugging her home and tracing her every move by radar, reports that she hears creaks or noises in the house that are caused by the ‘people’ who are stalking her, writes letters to members of parliament and governmental officials on a daily basis and enters chat rooms on the internet discussing the problems of her surveillance for hours on end. Then imagine a third person, who speaks with extreme rapidity and has a tendency to choose words that rhyme rather than completing a thought, who hears people talking to him even when he is alone and who believes that his thoughts are not his own but placed there by some outside entity. It is amazing that three people with such varying experiences could be suffering from the same disorder. Yet they would all receive a diagnosis of schizophrenia.
There is even heterogeneity in modern psychiatry’s diagnosis of schizophrenia which relies on two major classification systems, DSM IV and ICD10. While the DSM IV requires duration of symptoms for 6 month for a diagnosis of schizophrenia, the ICD10 requires only 1 month.

Fundamental research in the phenomenology of schizophrenia has supported a dichotomy of symptom profiles in schizophrenia (Strauss et al., 1974; Crow 1980; Andreasen and Olsen, 1982; Andreasen et al., 1982). It was believed that the positive symptoms such as hallucinations and delusions were prominent in the acute stage of schizophrenia (Type I) while the negative signs and symptoms were thought to prevail in the chronic stage of schizophrenia (Type II).

Positive symptoms are those which patients experience that make them different from others, such as hallucinations and delusions. The patient must report these symptoms - because they are not observable. They are closely linked with acute schizophrenia and are normally alleviated by neuroleptic drugs. The negative features exist when patients lack some element of normal behaviour, as seen in flattening of affect, poverty of speech and social withdrawal, and are usually associated with chronic schizophrenia. Because they are noted by some ‘absence’ of normal behaviour and are not dependant on the patient’s self reported symptoms, Frith (1992) suggests that the label ‘negative signs’ is more accurate than ‘negative symptoms’.

False beliefs that the patient firmly holds are known as delusions. For instance, a patient may believe the CIA or the police are looking for him for a crime that he has not committed or to help them with their investigations. Another patient may believe there is a bullet implanted inside her head, when in fact there is no entry wound, and she has
never actually been shot. Sometimes a patient may have a grandiose belief that he is a famous person or a religious entity. These delusions can be firmly held and the patient may make up long and involved stories to explain many parameters of his or her life in order to justify or explain the delusion.

Table 1.2. The Symptoms and Signs of Schizophrenia

<table>
<thead>
<tr>
<th>Positive Symptoms</th>
<th>Negative Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Thought insertion /thought withdrawal / thought broadcast</td>
<td>• Poverty of speech</td>
</tr>
<tr>
<td>• Thoughts spoken aloud/ thought echo</td>
<td>• Poverty of action</td>
</tr>
<tr>
<td>• Auditory hallucinations (third or second person)</td>
<td>• Social withdrawal</td>
</tr>
<tr>
<td>• Delusions of control and reference</td>
<td>• Flattened affect</td>
</tr>
<tr>
<td>• Paranoid delusions</td>
<td>• Avolition</td>
</tr>
<tr>
<td>• Stereotyped behaviour</td>
<td>• Catatonic behaviour</td>
</tr>
<tr>
<td>• Thought disorder (disorganised speech)</td>
<td></td>
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Hallucinations can be of any sensory modality, for example seeing things that are not present or experiencing unusual smells but are usually auditory. During auditory hallucinations a patient may hear voices talking about him/her in the third person, or the voices may speak to him/her directly or he/she may hear two or more voices discussing his/her movements or thoughts.
Thought disorder, or disorganised speech, is characterised by a speech pattern that is not fluent and difficult to understand. A patient may slip off track from one topic to another loosely related topic or choose words that rhyme rather than choosing words that complete a thought. Sometimes there is ‘pressure of speech’ and the patient speaks rapidly and compulsively and is difficult to interrupt.

Catatonic behaviour is extreme lack of movement. The patient may be frozen or locked into a position, even a seemingly uncomfortable position for hours.

An example of grossly disorganised behaviour would be dressing in a completely inappropriate manner - such as wearing only shorts and no shoes or shirt in the middle of winter, or saying things or doing things in public which are completely inappropriate, or collecting strange and worthless things. Perseveration refers to the intrusion of a response that was previously correct but is no longer relevant. When asked the day a person with schizophrenia may correctly answer ‘Tuesday’, and then when asked the month the patient might respond ‘Tuesday’ and when asked his favourite colour he might respond ‘Tuesday’. Although the patient understands the questions he is unable to inhibit that first response. Stereotyped movements (stereotypy) occur when a patient makes the same movement over and over again to no particular end, sometimes in a ritualistic manner insisting that something terrible will happen if the sequence is broken. An example would be a patient touching his glasses then his nose then his hair, then repeating this series three times in a row, over 100 times a day - with an apparent inability to inhibit the urge to repeat the sequence.

The negative signs include blunt affect, which is marked by lack of facial expression, and poor eye contact. Alogia is a restriction in the fluency of thought and speech,
noticeable by the one-word answers a patient may give to open-ended questions and a lack of additional information offered in conversation. A patient with severe negative signs may fail to bathe or change clothing daily and may have trouble completing tasks once started. He/she may also have few interests, or may not enjoy things as much as he/she used to, and suffer from an overall decrease in initiation of goal-directed behaviour (avolition).

These abnormal signs (patient’s behaviour) and symptoms (reports of mental state) can be brought on by other brain abnormalities such as tumours or drug abuse, but it is particularly in the absence of any such organic explanation that the diagnosis of schizophrenia is reached.

Neuroleptic medications are effective in the control of most positive symptoms, but negative signs are not usually affected by them. Although neuroleptic medication can produce side effects that resemble these negative signs, Kraepelin reported episodes of poverty of speech, poverty of action and asociality in people with ‘dementia praecox’ long before neuroleptic medicines were used. It is important to note that there is not a direct relationship between positive symptoms and negative signs. The ratings seem to be uncorrelated (Frith, 1992). Hemsley (1977) suggests that the negative signs of patients with schizophrenia are secondary to the ‘information overload’ which they experience. In order to adapt to the constant bombardment of information they develop these negative signs, such as poverty of speech and social withdrawal, as strategies to reduce the effects of the attentional impairment. But, more recent research has shown that on average, negative signs emerge a few years earlier than the positive symptoms but the patient is not diagnosed as suffering from schizophrenia until the positive symptoms are reported by the patient (Häfner and an der Heiden, 1997).
Liddle, (1995) suggests that the heterogeneity of schizophrenia is best described in terms of multiple dimensions of a single illness. Liddle (1987a,b, 1995) proposed that three subtypes of schizophrenia exist based on symptom type: psychomotor poverty, disorganization, and reality distortion. As the psychomotor poverty subtype greatly resembles the negative signs or symptoms of schizophrenia, Liddle effectively divided the positive symptom category into two distinct subtypes allowing for more emphasis to be placed on the disorganization of thought disorder. The exact quality and number of symptom dimensions in schizophrenia is still fervently debated. The different dimension of symptoms determined in a group of patients with schizophrenia depends on both the sample of patients tested and the collection of symptoms assessed (Johnstone and Frith, 1996). The positive symptoms are generally reported by the patient and are not confounded by movement or affect disorders. An auditory hallucination is rarely confused with a trait found in a healthy population. Negative signs can possibly resemble depression or the akinesia resulting from neuroleptic drugs. There is evidence of depression in schizophrenia both in first episode patients (Wassink et al., 1999; Koreen et al., 1993) and in chronic older patients (Zisook et al., 1999). Research has shown, however, that patients with high ratings of negative signs do not rank high on depression (Pogue-Guile and Harrow, 1984; Johnstone and Frith, 1996). Instead, ratings of hallucinations and delusions are more often linked with depressed state and suicidal ideas (Johnstone and Frith, 1996).

Carpenter and colleagues (1988) have further delineated the group of negative signs by suggesting that there are primary and secondary negative signs. The primary, or 'deficit symptoms' are the enduring, core negative signs of schizophrenia such as anhedonia and blunted affect. These signs are central to the diagnosis of schizophrenia and are
seen prior to, during, and after the onset of the positive symptoms. The secondary symptoms, however, are those negative signs that may be considered consequential to other symptoms or treatment of schizophrenia. For example, withdrawing to one's room all day because of avolition and asociality is different than withdrawing to one's room all day because one cannot stand to be around others because they constantly ‘read my mind’, ‘place thoughts inside my head’ and ‘say and think abusive things about me’. Thus the same behaviour, retreating to one’s room all day, can be either a deficit or a secondary symptom. When trying to determine the nature of the symptom the focus of the symptom (either primary or secondary) must be considered. Another example offered by Carpenter et al. (1988) is depression-induced anhedonia. The anhedonia should improve when the depression is treated, whereas primary anhedonia generally is not alleviated with medication. Thus the primary negative symptoms differ from the secondary symptoms in that they are less responsive to state changes, and thus are enduring traits of schizophrenia. Instead of positive and negative symptoms of schizophrenia, Carpenter et al. (1988) recommend the terms deficit and non-deficit schizophrenia. Deficit schizophrenia is demarcated by two or more ‘deficit’ symptoms which are present in an ‘enduring manner’ and include flattened affect, anhedonia, poverty of speech with curbing of interest and decrease in curiosity, lack of sense of purpose, and diminished social drive and these symptoms are not fully accounted for by depression, anxiety, medication effects, or environmental deprivation. Non-deficit schizophrenia would be traditional schizophrenia without the above symptoms. Both deficit and non-deficit schizophrenia may be found to include secondary symptoms.
1.2.5 Neurophysiological Heterogeneity

The structure of the brain in schizophrenia has been examined through imaging techniques and post-mortem examination. One common finding in imaging studies in schizophrenia is lateral ventricular enlargement (Weinberger, 1979a) yet there is at least one report of reduced ventricles in patients with schizophrenia (Andreasen et al., 1982). There have also been reports of widening of the third ventricle (Nyback et al., 1982) and cortical and cerebellar atrophy (Weinberger et al., 1979b, 1979c). Other findings suggest that compared to controls the brain in schizophrenia has smaller temporal-limbic volume (Suddath et al., 1989; Rossi et al., 1990; Andreasen et al., 1990; Breier et al., 1992; Bogerts et al., 1993), although others have not found differences between the two groups (Zipurski et al., 1994; Colombo et al., 1993). There is one report that basal ganglia volume is increased in patients with schizophrenia following exposure to typical neuroleptics and is decreased following exposure to atypical neuroleptics (Corson et al., 1999). When differences are found between patients and controls, they are seen on average, across large numbers of patients and the individual brain of a patient with schizophrenia may not appear different from a normal brain (Andreasen, 1984; Frith, 1992).

Post-mortem studies have reported differences between the brains of patients with schizophrenia and normal controls since Alzheimer (1897) reported cortical cell loss in patients with schizophrenia. More recent studies have found reduced volume of the hippocampus and amygdala (Bogarts et al., 1985) and increased striatal volume (Heckers et al., 1990). Some have found glial abnormalities in the brains of patients with schizophrenia (Jacob and Beckmann, 1986; Johnstone et al., 1994) while others have not (Roberts et al., 1986, 1987).
1.3 Diagnostic and Symptom Rating Instruments

In order to diagnose a person with schizophrenia, a clinician must use the diagnostic tools such as the DSM IV or the ICD10. However, for the most effective treatment or a thorough investigation a clinician or researcher commonly uses a rating scale to determine exactly from which of the many signs and symptoms a patient with schizophrenia is suffering. The Brief Psychiatric Rating Scale (Overall and Gorham, 1962) is a widely used rating scale, but it covers a wide selection of symptoms and is not designed to cover specific symptoms of schizophrenia in detail (Gur et al., 1991). There is an overlap among items, it lacks clear operational definitions, and there is not a clear link between the items on the scale and the symptoms of schizophrenia (Manchanda et al., 1989). In addition, Krawieka et al. (1977) point out that it is not sensitive to changes over time. Krawieka et al. (1977) wanted to create a scale that was short and easily administrable yet could be used reliably to assess chronic patients while being sensitive to any changes in symptom status. Previous scales other than the BPRS [the Wittenborn (Wittenborn, 1955), the Mental Schedule (Spitzer et al., 1964), the In-Patient Multi-dimensional Psychiatric Scale (IMPS) (Lorr et al., 1963), the Present State Examination (Wing et al., 1967), The Clinical Interview Schedule (Goldberg et al., 1970)] were considered too long to be useful as such an instrument (Krawieka et al., 1977). As a result a 5-point rating scale was created which was simple to administer, was sensitive to symptom changes in the patient, and was a reliable classification of patients according to Wing’s Scales. Half of the ratings are based on the patient’s replies to questions and the other half are based on the rater's clinical observation of abnormal phenomena. The Krawieka Manchester Scale is reported to provide the best compromise among conciseness, specificity of symptoms of schizophrenia, and sensitivity to change (Manchanda et al., 1989).
The Comprehensive Psychopathological Rating Scales (CPRS) as designed to rate items sensitive to change with treatment (Asberg et al., 1978). The scale is written with clear descriptions and guidelines for rating severity (Manchanda et al., 1989). It is longer than the Manchester scale and covers some of the positive and the negative symptoms of schizophrenia but also covers items that would not be considered primary symptoms of schizophrenia such as suicidal thoughts, sleepiness and aches and pains.

The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) was the first rating scale offering a thorough assessment of negative signs in schizophrenia (Andreasen, 1989). Poverty of speech, poverty of content of speech, affective blunting, avolition, ahedonia, and attentional impairment were combined to give a reliable rating of the 'negative' features of schizophrenia. The Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) allows for a comprehensive assessment and global ratings of hallucinations, delusions, positive formal thought disorder (derailments, tangentiality, incoherence and distractible speech) and bizarre behaviour. These two scales offer a complete set of rating scales to measure the signs and symptoms of schizophrenia that are sensitive to changes over time. Although these scales are longer than the Krawieka Manchester Scale (Krawieka et al., 1977) they offer more thorough coverage of the symptoms, but with practice can be administered relatively quickly.

Factor analytic studies from the Iowa Group have shown that the negative signs in the SANS, omitting attention and inappropriate affect, load as a single cohesive factor while the positive symptoms of the SAPS load on two main factors, disorganized symptoms (including inappropriate affect from the SANS) and florid psychotic symptoms (Andreasen 1983, 1984; Andreasen and Grove 1986; Andreasen and Olson, 1982;
Andreasen et al., 1995; Arndt et al., 1991; Miller et al., 1993) similar to the Liddle division (1987a,b).

Other rating scales have been developed over time. A few of the more prevalent are the Lewine, Fogg and Meltzer Scale, (Lewine et al., 1983), which combines items from the Nurses Observation Scale for Inpatient Evaluation (Honigfeld et al., 1966) and the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978); the Pogue-Geile and Harrow Negative Symptom Scale (1985), which is a negative symptom scale derived from the Behaviour Rating Schedule of the Psychiatric Assessment Interview (Carpenter et al., 1976); and the Positive and Negative Syndrome Rating Scale (PANNS) (Kay et al., 1992). Kay and colleagues (1992) developed the PANNS in order to provide a rating scale without a strict positive/negative dichotomy. The PANNS offers a 30-item scale for which the symptoms break down into four symptom complexes, negative, positive, excited and depressed. The PANNS is superior to the SAPS/SANS, according to Merriam, Kay et al. (1990) because of its "(1) standardized interview; (2) detailed operational criteria for all items at rating levels; (3) parallel assessment of positive, negative, and general symptoms to permit direct comparisons; (4) selection of 'primary' negative symptoms (Carpenter et al., 1985), which is essential for construct and content validity (Zubin 1985); and (5) intensive psychometric standardization that has supported the scale's inter-rater, retest, and internal reliability as well as the construct, concurrent, and predictive validity" (Kay et al., 1987, 1988) (p183).

Further analysis by the PANNS study group (White et al., 1997) used factor analysis on a sample of over 1,000 patients with schizophrenia, yet none of their models fit the data for such a large sample. Half of the subjects' data were used for reanalysis and the
group confirmed a five-factor model including positive, negative, dysphoric mood, activation, and autistic preoccupation.

With so many scales rating the different symptoms of schizophrenia comparisons of the more popular ones have emerged. Gur et al. (1991) examined the reliability of the BPRS, the SANS/SAPS and Carpenters deficit/non-deficit distinction. One drawback of the BPRS is that it tends to give an overall rating of severity of schizophrenia rather than specifying the symptom profile of the patient (Gur et al., 1991). The SANS/SAPS and the BPRS measured corresponding dimensions of schizophrenia symptomatology without direct overlap. Cluster analysis revealed that most patients with low negative symptom scores had non-deficit syndrome, whereas patients with high negative symptom scores had deficit syndrome. Dollfus and Brazo (1997) used cluster analysis to compare the SANS/SAPS and the PANNS. Both sets of scales produced a four-cluster solution, with positive, negative, mixed and mild clusters. Further analysis of these data revealed a five-cluster solution, which divided the positive cluster into a disorganized and a non-disorganized cluster on both sets of scales. Based on the findings of comparison studies the different scales are generally reliable and valid, although some discrepancies exist (Fenton and McGlashan, 1992), for example the SAPS/SANS includes attention as a ‘negative’ sign whereas it is not classified as such in the PANSS or BPRS. Because the subtype classification is still hotly debated, i.e., positive/negative, deficit/non-deficit, psychomotor-poverty/psychotic/disorganized, the rating scales appear to be most useful for symptom ratings rather than a subtype classification.
1.4 Physiological Hypotheses of Schizophrenia

1.4.1 Dopamine Hypothesis

It has been suggested that the positive symptoms of schizophrenia are caused by increased dopaminergic activity in the brain (Wright and Woodruff, 1995). The "dopamine hypothesis" (Randrup and Munkvad, 1972) is supported by the effectiveness of neuroleptics which are dopamine antagonists at treating some of the positive symptoms of schizophrenia and the fact that dopamine-releasing amphetamines can cause schizophrenic-like symptoms such as paranoia and hallucinations. Parkinson's disease is a movement disorder with tremor, akinesia and rigidity as the cardinal symptoms. Schizophrenia and Parkinson's disease share certain symptoms such as akinesia (poverty of action) and bradykinesia (slowness of movement initiation and execution). The symptoms of Parkinson's disease are caused by a dopamine deficiency in the substantia nigra and putamen (Gotham et al., 1988) and replenishing dopamine through medication alleviates the symptoms (Birkmayer et al., 1974). Sometimes giving the patient with Parkinson's disease too much dopaminergic medication will result in schizophrenia-like symptoms, such as hallucinations. One suggestion is that in schizophrenia there is an underactive dopaminergic system in the dorsolateral prefrontal cortex coupled with increased subcortical dopaminergic activity in the striatum (Weinberger et al., 1991). The reduced frontal dopamine may lead to the negative signs that resemble those seen in Parkinson's disease, while the increased dopamine in the striatum may lead to the positive symptoms. Another possibility is that the dopamine receptors are more sensitive in schizophrenia. In partial support of this view, Okubo et al. (1997) have reported that in patients with schizophrenia, the binding of a radioactive tracer to dopamine receptors (D1) is reduced in the prefrontal cortex. This reduction was linked to both the severity of negative signs and impaired performance on the
Wisconsin Card Sorting Task (WCST) a task believed to depend on the integrity of the dorsolateral prefrontal cortex for its normal performance (Weinberger et al., 1986).

1.4.2 ‘Hypofrontality’ hypothesis

Another hypothesis related to the dopamine surplus and deficiency hypothesis is that of ‘hypofrontality’. Negative signs and involuntary movements are also observed in individuals with subcortical lesions (e.g. basal ganglia and thalamus) (Pantelis and Nelson, 1994). Damage to the supplementary motor area (SMA) (Dick et al., 1986; Deecke et al., 1985) and the anterior cingulate (Devinsky et al., 1995) are also associated with increased poverty of action. Based on the surface similarity of symptoms, schizophrenia has been linked to a dysfunction within the frontal lobes.

Various regions of the basal ganglia are now known to be connected with different regions of the prefrontal cortex (Alexander et al., 1986). Alexander et al. (1986) have identified five circuits linking the frontal lobes with the basal ganglia via different thalamic relays. These 5 circuits are shown in Figure 1.1. In the so-called ‘complex or associative circuit’, the caudate nucleus projects to the dorsolateral prefrontal cortex via the ventral anterior thalamic nucleus. This circuit is considered to be associated with executive function (Cummings, 1995). Thus, damage anywhere in this circuit is considered to result in impairment of executive function. Examples of such damage would be poor recall but intact recognition, perseveration, difficulties in set shifting, impaired response inhibition – many of which are seen in schizophrenia.

In the ‘motor’ circuit projections stem from the SMA, premotor area and the motor cortex to the putamen and then on to the globus pallidus and substantia nigra and then to
the ventral part of the thalamus before projecting back to the SMA. It has been suggested that this circuit plays a part in initiation of internally-generated movements (Alexander et al., 1986).

The 'anterior cingulate' or 'limbic' circuit connects the anterior cingulate cortex and the ventral striatum via the medial dorsal nucleus of the thalamus. This circuit is considered to be involved in regulation of motivation (Cummings, 1995). Damage to this circuit results in apathy, reduced motivation, concentration and impaired inhibition.

Impairments such as apathy, poverty of action, perseveration or impaired response inhibition are associated with dysfunction of several of these circuits. These circuits are regulated by several neurotransmitters including dopamine, serotonin and acetylcholine (Cummings, 1995). Decreased or increased dopamine in one part of a circuit could potentially alter the efficient functioning of the whole circuit. Thus, some of the cognitive deficits seen in schizophrenia, especially those associated with negative signs may be linked to impaired dysfunction of complex, motor, or limbic circuits.
Figure 1.1 Proposed Cortical-Basal Ganglia - Thalamic - Cortical Loops from Alexander et al. (1986)

The five circuits showing projections from specific areas of the frontal cortex to discrete areas of the striatum which project back to the originating frontal areas via distinct output sections of the basal ganglia and the thalamus. Abbreviations are as follows: ACA: anterior cingulate; APA: arcuate premotor area; caudate, (b) body, (h) head; DLC: dorsolateral prefrontal cortex; EC: entorhinal cortex; FEF: frontal eye fields; GPi: internal segment of the globus pallidus; HC: hippocampal cortex; ITG: inferior temporal gyrus; LOF: lateral orbitofrontal cortex; MC: motor cortex; MDpl: medialis dorsalis pars paralamellaris; MDmc: medialis dorsalis pars magnocellularis; MDpc: medialis dorsalis pars parvocellularis; PPC: posterior parietal cortex; PUT: putamen; SC: somatosensory cortex; SMA: supplementary motor area; SNr: substantia nigra pars reticulata; STG: superior temporal gyrus; VAmc: ventralis anterior pars magnocellularis; VAp: ventralis anterior pars parvocellularis; VLM: ventralis lateralis pars medialis; VLO: ventralis lateralis pars oralis; VP: ventral pallidum; VS: ventral striatum; cl-caudalateral; cdm-caudal dorsomedial; dl-dorsolateral; ld-lateral; ldm-lateral dorsomedial; m-medial; mdm-medial dorsomedial; pm: posteromedial; rl-rostrodorsal; vd-rostrolateral; vm-ventromedial; vl-ventrolateral.
Studies of regional cerebral blood flow (rCBF) have provided some support for the hypofrontality hypothesis. For normal controls frontal rCBF increases in the dorsolateral prefrontal cortex during the WCST. Patients with schizophrenia perform poorly on this task and also fail to show increased rCBF in the dorsolateral prefrontal cortex (Weinberger et al., 1986; Seidman et al., 1994). In a study on discordant monozygotic twins Berman et al. (1992) found that each of the twins with schizophrenia showed less activation of the dorsolateral prefrontal cortex during the WCST than the unaffected twin. In the Tower of London task, another test that activates the prefrontal cortex, patients with schizophrenia perform poorly and those with a higher rating of negative signs do not show the increased rCBF in the frontal areas as compared to normal controls (Andreasen et al., 1992). Other studies have shown that increased hypofrontality is linked with higher positive symptoms such as delusions and that the degree of hypofrontality is reduced when these symptoms remit (Spence et al., 1998). Patients with schizophrenia also show a general hypofrontality (lower anterior-posterior gradient) compared to controls (Schroeder et al. 1994; DeLisi et al., 1995). Patients with schizophrenia with negative signs have reduced activation of the dorsolateral prefrontal cortex (Liddle et al., 1992; Wolkin et al., 1992) and smaller prefrontal volume (Breier et al., 1992) while schizophrenia with disorganisation syndrome have reduced activation of the anterior cingulate (Liddle et al., 1992). Across all subtypes of schizophrenia parahippocampal rCBF impairment has been reported (Friston et al., 1992). Patients with schizophrenia have also shown decreased activation in the sensorimotor cortex and the SMA on a finger to thumb opposition task (Schroder et al. 1995) and pronation/supination wrist movements (Schroder et al., 1999). However, in a verbal fluency task that was paced so that each group produced the same number of responses, patients with schizophrenia did not show hypofrontality (Frith et al., 1995).
1.5 Cognitive-Anatomical Models of Schizophrenia

Due to the heterogeneous nature of schizophrenia, there is not one particular hypothesis or theory that is accepted universally as the definitive explanation of all the signs and symptoms. More than 100 years after Kraepelin first explored the disorder schizophrenia is not fully understood. Schizophrenia manifests itself in many different ways and as a result there have been many different attempts to explain exactly what is happening in these people who, we say, are suffering from schizophrenia. A number of cognitive-anatomical theories have been proposed to explain the symptoms of schizophrenia, four of these theories will be briefly considered. These four models are considered because they approach the immense task of explaining schizophrenia by examining the symptoms from which the people with schizophrenia suffer and then attempting to interpret the symptoms through an underlying cognitive theory. The anatomical substrates supporting the theories are important, but first we need to be able to explain why one patient's symptoms differ so greatly from another and also explain how one patient's symptoms can vary so greatly over time. These four theories examine the symptoms by using experimental paradigms to attempt to determine what is happening in the patient with positive symptoms and/or the patient with negative signs. These are the theories of Hemsley (1987), Gray et al. (1991) Gruzelier (1984), and Frith (1987, 1992).

1.5.1 Hemsley's (1987) Cognitive Model

In order to explain the heterogeneity in the phenomena and neuropathology of schizophrenia Hemsley (1987, 1977, 1994) suggests that the behavioural and experiential abnormalities in schizophrenia are due to a breakdown in the connection
between stored information and existing sensory input. It is in the interaction of stored memories and perception of current stimuli that the problems of schizophrenia arise.

Figure 1.2 Model of cognitive abnormalities and symptoms of schizophrenia (from Hemsley, 1987, 1994)

Thus, according to Hemsley, the fundamental problem in schizophrenia is a disturbance in perception. The influence of spatial and temporal regularities is weakened coupled with a problem of material, normally just beyond the realm of focus, intruding into the mind of the patient with schizophrenia (Hemsley, 1987). Memories are stored correctly, according to Hemsley, but the automatic assessment of the relevance or the irrelevance of features of sensory input is impaired, and as a result the patient with schizophrenia is bombarded with 'ambiguous, unstructured sensory input' (Hemsley, 1994). The end result would be the positive symptoms seen in schizophrenia like paranoia. With this faulty system, things that should seem familiar may appear unfamiliar and things that should be irrelevant may seem relevant. According to Hemsley (1994) two paradigms
that have been studied both in animals and humans offer good examples of these abnormalities.

Latent inhibition (LI) is a phenomenon first described by Lubow et al. (1982). After a mouse has been exposed to a stimulus (such as a tone) it learns a stimulus-reinforcement pairing (whenever there is a tone, there is also a food pellet) much slower than a mouse not pre-exposed to that stimulus (Lubow et al. 1982). This same phenomenon is seen in normal healthy humans, and in chronic medicated patients with schizophrenia, but it is not seen in patients with acute schizophrenia (Baruch et al. 1988). An individual with acute schizophrenia who is pre-exposed to a stimulus notices the stimulus-reinforcement pairing as quickly as the patient with schizophrenia with no pre-exposure. According to Hemsley (1994), less attention is allocated to this 'predictable redundant stimulus' than the amount allocated if the stimulus is new. As less attention is allocated to the redundant stimulus, the person pre-exposed to the stimulus requires longer to notice the stimulus is paired with the reinforcement than a person who was not pre-exposed. Thus, in schizophrenia, there must be a deficit in the individual's ability to reduce or inhibit the attention allocated to a redundant stimulus. There is evidence that dopamine plays an important role since, in animal studies using the LI paradigm dopamine agonists such as amphetamine reduce stimulus-reinforcement detection time (Solomon et al. 1981). The phenomenon of LI returns if neuroleptics are administered to block dopamine (Feldon and Weiner 1991).

The Kamin blocking effect (Lubow 1982) provides similar results. In this paradigm a stimulus e.g. buzz is paired with another stimulus e.g. light in a pre-exposure phase. In a second phase the pre-exposed group and a naive group are subjected to a compound stimulus e.g. buzz and bell paired with the light stimulus. When the relation between
the bell and the light is tested the pre-exposed group learns more slowly than the naïve
group. This delay in learning is not seen in animals given amphetamine (Crider et al.,
1982) and is reduced in patients with acute schizophrenia (Jones et al., 1992).

With both of these paradigms, patients with schizophrenia are not experiencing
interference from the original exposure. This could be a failure of memory - the patient
with schizophrenia simply fails to remember that the buzz was previously paired with
the light, so in the second phase all the stimuli are as new to him/her as they are to
individuals not pre-exposed. Alternatively the deficit could be due to a limited
attentional system (e.g. Hirt and Pithers, 1991). A large system may hold 'X' on line
leaving enough space to handle peripheral input as well. This system may be distracted
by multiple input. A smaller system may be able to hold 'X' on line, but its capacity is
fully used and thus any other information or input is not accepted, or noticed or put ‘in’.
If a person with schizophrenia has a smaller capacity the redundant information is
simply never recognised as relevant information. Either way, from Hemsley’s point of
view, the inability to correctly register the new stimulus - response pairing is
fundamental to the problems seen in schizophrenia. This could explain, from our
example, the links our patient makes between the creaks of the house and the ‘people’
Spying on her, instead of linking the creaks she hears to previous creaks that have been
present on windy evenings.

1.5.2 Gray et al.’s (1991) Anatomical Model

Hemsley’s model is closely linked with Gray et al.’s (1991) anatomical model
accounting for the positive symptoms of schizophrenia, which centres on the functions
of the septohippocampal system (including the hippocampus, the subicular areas and the
cingulate cortex) and the motor functions of the basal ganglia. (See Figure 1.3). Gray et
al. (1991) propose that the caudate motor system (including the motor cortex, the caudate-putamen and the substantia nigra) encodes the content of each step in a motor program, while the accumbens system (ventral striatum and limbic cortex) works with the caudate to engage switching from one step in a motor program to the next. The caudate and accumbens systems also regulate behavioural responses to novel stimuli. The septohippocampal system surveys the outcome of a motor step to see if it corresponds with the expected outcome and then relays this back to the ventral striatum. Projections from the amygdala to the ventral striatum regulate the motor program and also transmit information about stimulus/response associations. The prefrontal cortex oversees the system by regulating the activities of the caudate, accumbens and septohippocampal systems.

Figure 1.3 Anatomical model of cognitive function (adapted from Gray et al., 1991)
Administering amphetamine causes increased release of dopamine throughout the basal ganglia causing disruption to the subicular input to the accumbens. According to Gray et al., this would then interfere with the smooth running of motor programs and all their intermediary steps resulting in the motor output of the striatal systems being controlled by other means. One of the possible alternatives suggested by Gray et al. (1991) is that one movement or series of movements may take precedence over any others and occur repetitively due to continued activity in the feedback loops between the caudate and accumbens. Examples would be the stereotyped movements seen in amphetamine-treated animals, and individuals with schizophrenia. Also, disruption of the input from the subicular area to the ventral striatum impairs the transition between motor programs. The authors suggest the resulting behaviour would be that a person’s attention would be drawn towards novel stimuli or familiar stimuli will appear to be novel and treated as such, which is also seen in schizophrenia.

Cools and Ellenbroek (1991) point out that while the striatal and accumbens systems are responsible for switching motor programs, they may not work ‘in tandem’ as Gray et al. (1991) suggest. According to research the striatal system is involved in the switching mechanism in non cue-directed (or self-initiated) behaviour (Cools 1980, Cools et al., 1990) while the accumbens system is involved in the switching mechanism for cue-directed behaviour (Cools et al., 1990). Thus, the two systems oppose each other ‘more like a seesaw’ (Cools and Ellenbroek, 1991).

The models of both Hemsley (1987) and Gray et al. (1991) attempt to offer an explanation of the positive symptoms of schizophrenia - especially behaviours such as perseveration, stereotypy, thought disorder and paranoia. Because the individual with schizophrenia has difficulty making successful connections between the current state of
the environment and previous experiences he or she produces behaviours or reactions which, to the rest of us, appear odd. In the case of paranoia he or she sees coincidences where none exist. In thought disorder a patient may choose to speak using words which rhyme and are therefore linked phonetically rather than choosing words linked semantically and would make sense. Because no alternative motor program is generated, the stereotyped movement of touching one’s nose, then one’s glasses and then one’s hair is repeated over and over hundreds of times each day. There is a lack of inhibition to control these inappropriate behaviours. Both these models, however, do little to account for the negative signs in schizophrenia, which are so debilitating and so prevalent. The Cerebral Lateralization Hypothesis (Gruzelier, 1984) and Frith’s (1992) model address the negative signs more directly.

1.5.3 Cerebral Lateralization Hypothesis (Gruzelier, 1984, 1991)

1.5.3.1 Cognitive evidence

It has been proposed that the two syndromes in schizophrenia are characterised by opposite asymmetries in hemispheric activation (Gruzelier, 1984; Gruzelier, 1991). Hemispheric specialization is fundamental to this theory and proposes that the left hemisphere is linked with accelerated cognition, speech production and increased behavioural activity and the right hemisphere is linked with negative affect (Gruzelier et al., 1995). The ‘Active Syndrome’ has been associated with higher left hemispheric activation than right and is characterized by the positive symptoms of behavioural over activity, pressure of speech, grandiosity, paranoia, inappropriate affect, affective delusion (Gruzelier 1999). The ‘Withdrawn Syndrome’ is associated with higher right hemispheric activation than left and is characterized by the negative signs such as social withdrawal, flattened affect, poverty of speech and motor retardation (Gruzelier et al., 1999). A third syndrome, Schneiderian, not associated with laterality coexists with the
other two and consists mainly of hallucinations (Gruzelier 1999). The Active and Withdrawn Syndromes are linked with cognitive impairment, namely the active syndrome is associated with poorer spatial than verbal performance whereas the Withdrawn Syndrome is associated with poorer verbal than spatial performance (Gruzelier et al., 1988). Further evidence of this active-withdrawn asymmetry has been shown in schizotypal personalities of normal subjects (Gruzelier, 1994; Gruzelier et al., 1995). Individuals with a face-memory (a right hemisphere task) advantage on the Warrington Memory Test (Warrington, 1984) displayed evidence of Withdrawn Syndrome features such as flattened affect and few close friends while individuals with a word-memory advantage (a left hemisphere task) showed a tendency toward the Active Syndrome features, albeit weak, of odd speech. Furthermore, a single case study revealed that a male student displayed a strong (extreme outlier) face-word discrepancy prior to a first episode of schizophrenia and when later diagnosed with schizophrenia presented with the Withdrawn and Schneiderian syndromes as would be expected by his face-memory results (Gruzelier et al., 1995). In patients with schizophrenia males but not females showed a word advantage in recognition memory in the active syndrome whereas both sexes show a face recognition advantage in the withdrawn syndrome (Halgren et al., 1994, Burgess and Gruzelier, 1997a, b). Longitudinal studies show that the effects of memory deficits and their relation to the Active and Withdrawn Syndromes change over time such that patients with Active Syndrome and a face disadvantage showed a face advantage at a later testing time when they were suffering from the Withdrawn Syndrome (Gruzelier 1999). There is evidence that patients with schizophrenia are impaired in both temporohippocampal and frontohippocampal tests of learning and memory (Hebb's digit test, the Corsi block-span test and Petrides test of spatial and non-spatial conditional learning test) (Gruzelier et al., 1988). The hemispheric specialization in patients with schizophrenia was similar to results seen in a
previous study investigating performance of neurological patients with left or right hemisphere lesions (Milner 1982). The schizophrenia patients with lower left than right hemisphere activation had similar performances to neurological patients with left hemisphere lesions and schizophrenia patients with lower right than left activation had results comparable to those of the right lesioned neurological patients (Gruzelier et al., 1988).

1.5.3.2 Psychophysiological Evidence

The asymmetry syndromes were based on data-driven findings from research on electrodermal orienting responses (Gruzelier 1981, Gruzelier and Manchanda 1982). Skin conductance was measured on the fingers while the subject listened to tones. The onset of the orienting response was approximately 1-5 s after the tone and habituation was considered to have occurred when there was an absence of responses on two successive trials. Laterality was determined by the mean response amplitude: right-left ÷ right + left (Gruzelier and Davis 1995). Greater left than right activation was found in patients with the positive symptoms of the Active Syndrome and greater right than left hemispheric activation was found in the patients with the negative signs of the Withdrawn Syndrome (Gruzelier 1981, Gruzelier and Manchanda 1982).

Further physiological evidence for the asymmetry in schizophrenia exists. Lateral eye movements occur controlaterally to the more activated frontal eyefield (Gruzelier, 1999) and studies have shown that patients with the Withdrawn Syndrome had more left-sided eye movements while patients with the Active Syndrome had an increased number of right-sided eye movements (Gaebel et al., 1986). The Hoffman reflex is an index of spinal motor asymmetry and reduced motoneuron excitability (Tan and Gurgen 1986). Using this index, right hemisphere dominance was found to be associated with the
symptoms of the Withdrawn Syndrome, while left hemisphere dominance was found to be associated with the symptoms of Active Syndrome (Goode et al., 1981). However, one study found right asymmetry in a sample of patients with schizophrenia with both the Active and the Withdrawn Syndromes (Tan and Gurgen, 1986). Studies using EEG have found that a reduction in alpha activity, indicating greater activation, of the right hemisphere was associated with symptoms of the Withdrawn Syndrome (Merrin and Floyd, 1992) and reduction in alpha activity of the left hemisphere was associated with symptoms of the Active Syndrome (Coger and Serafetinides, 1983).

Thus a number of different physiological measures have shown asymmetry in the hemispheric functioning of patients with schizophrenia. Greater activation of the right than left hemisphere is associated with symptoms of the Withdrawn Syndrome while increased activation of the left hemisphere compared to the right hemisphere is associated with symptoms of the Active Syndrome. Furthermore, the results of cognitive tasks that are hemisphere related have added more credence to the delineation of the schizophrenia into Active and Withdrawn Syndromes. However, a patient suffering from either of these syndromes may also show symptom of the Schneiderian Syndrome. While the Cerebral Lateralization theory does a much better job at addressing the negative signs of schizophrenia than Hemsley’s (1987) or Gray’s (1991) models, this theory does not explain the basis of the Schneiderian symptoms, other than to report that they are not hemisphere specific and may co-exist with either of the other two syndromes.
1.5.4 Frith’s (1987, 1992) Neuropsychological Model

1.5.4.1 Dysfunction of Willed Actions

A fourth theory attempts to explain the signs and symptoms of schizophrenia, including all the positive symptoms, both ‘active’ and ‘Schneiderian’ as well as the negative signs. Frith (1992) has suggested that the signs and symptoms of schizophrenia such as poverty of action, stereotyped action and incoherent action reflect a dysfunction of “willed” actions while the processes involved in “stimulus driven” actions remain largely intact. Willed actions are purposeful, goal-directed behaviours. They are defined as actions that are not directly evoked by external stimuli but depend on internal control (Frith 1992). However, even when there is an external trigger for the initiation of an action there may be certain processes that depend on internal control (Jahanshahi and Frith, 1998).

Frith’s (1992) model distinguishes between two routes to action. In the stimulus driven route, perception of the stimulus leads to an intention to act by responding to that stimulus. In the willed action route, goals lead to willed intentions that result in actions. (See Figure 1.4). In schizophrenia there is an inability to turn goals and plans into actions. In patients with negative signs this impairment exhibits itself in poverty of willed intentions, thus limited action. In patients with positive signs this impairment exhibits itself as impaired inhibition of stimulus driven action. It is proposed that patients with schizophrenia particularly those with negative signs, should have an impaired ability to generate action at will, but stimulus-driven behaviour should be intact.

This hypothesis is partially supported by the symptoms of the disease. Patients with schizophrenia can perform routine acts elicited by environmental stimuli, but have
difficulty in producing spontaneous behaviour in the absence of external cues. This is seen most clearly in the negative signs such as poverty of speech and poverty of action. Similar deficits are seen in monkeys with lesions to the SMA and the cingulate cortex that are impaired on the self-initiated task of raising an arm. Yet, these same animals are able to complete the task if there is an external stimulus such as a tone to cue the behaviour (Passingham, 1993). The negative signs of schizophrenia can be compared to the lack of movement seen in individuals with Parkinson’s disease. Patients with Parkinson’s disease have trouble initiating actions, but the will to act and the formulation of a plan are intact, the impairment lies in their ability to execute the desired action. In schizophrenia, however, it is the ability to turn a plan or goal into a willed intention that is impaired.

Figure 1.4 Stimulus driven and willed actions from Frith (1992). Possible loci of impairments in positive symptoms in schizophrenia (failure of inhibition), negative signs in schizophrenia (failure to generate willed actions) and Parkinson’s disease (goals, plans and willed intentions are intact, but ability to initiate action is impaired).
According to Frith (1992) a person with no ability to initiate an activity spontaneously is left with three options. The first is to do nothing; this is reflected in schizophrenia as poverty of action. The second is to repeat the last movement; this is known as perseveration, which is also seen in schizophrenia. The third is to respond to an external stimulus even though it may be irrelevant. This is seen in the inappropriate actions by individuals with schizophrenia such as a patient may comment a person’s tie or hair or some other stimulus in the room in mid conversation rather than continue with the conversation.

The individual with schizophrenia is responding to many different, inappropriate stimuli from the environment instead of spontaneously initiating actions or thought processes. The end result is stimulus-driven behaviour. The disorganised behaviour seen in schizophrenia could be due to an inability to inhibit inappropriate responses. This failure of inhibition would also apply to perseverative behaviour, since the most recent response is always the easiest to choose, but is normally inhibited, as it is very rarely appropriate to repeat one’s last action.

Three classes of decision precede a voluntary action: 'what to do'- selecting an action among a set of possibilities, 'how to do it' - developing a strategy, and 'when to do it'-deciding the precise moment to begin (Kornhuber et al., 1989). Different criteria are relevant to defining an action as more or less volitional, for example intentionality, choice and control, attention and conscious awareness (Jahanshahi and Frith 1998). In a recent review of evidence, Jahanshahi and Frith (1998) provided support for a willed action system based on the fronto-striatal circuits. Various functional imaging studies have revealed that compared to rest, random movement is associated with greater activation of the dorsolateral prefrontal cortex and the anterior cingulate (Frith et al.,
1991; Playford et al., 1992), the lateral premotor cortex and the left putamen (Playford et al., 1992). During learning of a new motor sequence, the dorsolateral prefrontal cortex, the anterior cingulate and the striatum are activated (Jenkins et al., 1994; Jueptner et al., 1997). If selecting when to respond the right dorsolateral prefrontal cortex, the anterior cingulate and the anterior SMA bilaterally (Jahanshahi et al., 1995) and the loop between the putamen, the ventrolateral thalamus and the SMA (Rao et al., 1997) are activated. Advance preparation of movement is associated with activation of the SMA, the lateral premotor cortex and the anterior cingulate (Deiber et al., 1996) while both response initiation and suppression of movement are associated with activation of the anterior SMA (Humberstone et al., 1997). Thus certain frontal cortical (dorsolateral prefrontal cortex, anterior cingulate, SMA) and subcortical (thalamus and basal ganglia) areas of the brain are activated during willed action.

1.5.4.2 Impaired Self-Monitoring

We are able to detect that, as we move our eyes, it is our eyes moving and not the external world. Helmholtz (1866) proposed that the 'corollary discharge' acts as a message to let our system know that it is not us, nor our surroundings that are moving, but only our eyes. This corollary discharge enables us to monitor which movements are our own and which are movements of the environment. There is some process by which I recognise that it is in fact me thinking some thought and there is not someone else placing it in my head, or it is me lifting my arm and not some other entity lifting it for me. By the age of 5, children can detect that the doctor hitting the knee caused a knee jerk and that is was not a movement that the child intended. Children younger than 5 make no distinction between the two (Shultz et al., 1980). Thus, there is a point during development when self-monitoring of self-generated actions develops. The areas of the brain that seem to be involved in corollary discharge are the frontal eyefields and the
anterior cingulate cortex (Frith, 1992). These areas may play a role in allowing us to
detect whether or not movements are self-initiated or generated by an external source.

According to Frith (1992), besides impairment of willed actions, a second and linked
problem in schizophrenia is impairment of self-monitoring. One symptom of
schizophrenia is hearing voices - auditory hallucinations. Studies have shown that quite
often it is the patient’s inner speech that is heard and described as another’s voice. The
patient fails to detect the inner speech or thoughts as his or her own. Once again this is a
failure of ‘will’. The patient does not recognise that the thought is of his or her own
‘will’ and therefore attributes it to an outside entity. In support of this, a PET study on
patients with schizophrenia who suffered from auditory hallucinations has shown that
those with ‘active’ hallucinations have reduced activation in the left middle temporal
gyrus and the rostral supplementary motor area, areas normally activated during inner
speech (McGuire et al., 1996b), compared to normal controls and patients with
schizophrenia not prone to auditory hallucinations (McGuire et al., 1996a).

Other symptoms may result from impaired self-monitoring. One example is thought
insertion, if the thought is not recognised as originating in one’s own mind then
someone or something else must have placed the thought there. Another example is
delusions of control, if one does not recognise a particular act as being initiated by one’s
own will, then some other force could be perceived erroneously as the agent causing the
patient to do or say something. There is evidence that patients experiencing symptoms
of alien control are impaired on self-monitoring tasks and this impairment is
independent of neuropsychological or cognitive function (Stirling et al., 1998). A third
example would be perseveration. It has been shown that hallucinating patients with
chronic schizophrenia produce more perseverative and inappropriate incorrect responses
during a word recognition test (Done and Frith, 1984) and more stereotyped sequences with perseveration in a two choice guessing task (Frith and Done, 1983).

These results suggest that patients with schizophrenia are impaired at the level of monitoring their actions and attributing them as being internally generated.

1.6 General Aims of Thesis

Schizophrenia is a heterogeneous disorder. The symptoms from which patients with schizophrenia suffer differ greatly among patients and also differ within a single person across time. If we are to determine what causes schizophrenia, if it is in fact one single disorder, and if we are to treat schizophrenia successfully, we need to determine what is actually happening in the brains and minds of the people who have what we currently call schizophrenia. Four different theories have been presented which attempt to explain the phenomena of schizophrenia. While two (Hemsley, 1987 and Gray, 1991) present strong cases for the possible underlying substrates in the positive symptoms such as paranoid delusions and perseveration, they do nothing to explain the debilitating negative signs that are prevalent in schizophrenia. A third theory (Cerebral Lateralization) addresses the negative signs, ‘Withdrawn Syndrome’, with both cognitive and psychophysiological evidence, while explaining some of the positive symptoms such as pressure of speech and thought disorder, ‘Active Syndrome’, but does not successfully explain the ‘Schneiderian’ symptoms such as commentary hallucinations, delusions of control and thought insertion, other than that these symptoms can co-exist with the Active or Withdrawn Syndrome. Frith’s (1992) neuropsychological model of schizophrenia, however, attempts to address all of the positive symptoms and all the negative signs by suggesting that the symptoms that patients with schizophrenia experience are caused by a fundamental problem in the
initiation and monitoring of willed action. The studies presented here focus on the investigation of negative signs because they are debilitating, poorly understood and rarely studied. The purpose of this thesis is to examine one aspect of Frith's (1992) cognitive neuropsychological model of schizophrenia, more specifically the hypothesis that some of the impairments seen in schizophrenia are in fact due to impairment of willed actions while stimulus driven actions remain intact. This will be done by investigating aspects of willed performance in patients with schizophrenia, first by examining willed action in schizophrenia through studies of movement initiation, and then by examining willed action in schizophrenia through studies of willed suppression.

1.7 General Approach to Statistical Analysis

Preliminary data analysis included assessing the distribution of the variables for normality, outliers and skewness. If any subject's data indicated outlying values on multiple variables, the data were omitted from the analysis. This is stated in the text where it occurs. Each study had either a mixed between-groups and within-subjects design or a simple between groups design. The data were analysed using repeated measure analysis of variance or one way analysis of variance and covariance respectively. The between subject variable was Group (patients vs controls) except for Study 3, Study 4 and Study 5, in which there were three groups (controls and two patient groups). The within subject variables differed in each study and are explained in more detail in the Methods section of each study.

Where necessary, to deal with violations of assumptions of sphericity, the Greenhouse-Geisser epsilon was used to adjust the degrees of freedom. Pre-planned special contrasts were carried out where appropriate. Post hoc tests included independent t-tests and paired t-tests, which were used as required.
Comparisons of the characteristics of the groups were carried out using independent t-tests for age, education level, handedness, and depression scores, while the chi square test was used to determine sex differences between groups. In each study the individual symptom ratings were correlated with key variables using Pearson’s correlation coefficients. Partial correlations were carried out controlling for medication, depression and cognitive impairment. Bonferroni adjustments controlling for the number of correlations were made. All statistics were carried out using SPSS for Windows version 8.0.

1.8 Patient Selection

In all studies all patients met the criteria for diagnosis of schizophrenia according to the DSMIV. Patients were recruited from three sources: (i) referred by Professor Maria Ron (ii) recruited from the Maudsley Hospital Register or (iii) were volunteers recruited from an advertisement placed in the National Schizophrenia Bulletin. The diagnosis of schizophrenia was confirmed in all referred cases by consulting hospital notes. For the 7 volunteers recruited by advertisement, the name of their GP or clinician was obtained and the diagnosis of schizophrenia was confirmed. None of the patients had any prior history of head injury, neurological or physical illness.

Each subject’s mental state was measured by the Mini Mental State examination and none scored below the cut off indicative of cognitive impairment (score below 25, Anthony et al., 1982). Duration of illness ranged from 3 to 27 years. The patients recruited from the three sources did not differ in terms of demographic or disease-related features.
The details of the patients and controls including sample size, handedness, male to female ratio, mean age and patient symptom ratings are given in the Methods section for each study.
CHAPTER 2

Study 1: Impairment of Willed Actions and Use of Advance Information for Movement Preparation in Schizophrenia

2.1 Introduction

One way of testing the hypothesis of impairment of willed actions in schizophrenia is to examine the speed of response initiation in reaction time (RT) tasks that differ in the extent to which they require volitionally prepared versus stimulus-driven responses. In simple RT (SRT) tasks the same stimulus is presented across trials, and requires the same invariable response. The stimulus-response invariance provides the subject with the option of preparing the response before presentation of the stimulus, that is to preprogramme it. In SRT, this preprogramming is an optional and volitional process, which has been shown to require attention as it is susceptible to interference from the concurrent performance of a secondary task (Frith and Done, 1986; Goodrich et al., 1989). In contrast, in an uncued choice RT (CRT) task, where there are several stimuli each indicating a different response, the response is elicited by presentation of the imperative stimulus. In uncued CRT, the response is selected and programmed after presentation of the stimulus, so it is considered to be stimulus-driven. Volitional preprogramming is not possible in uncued CRT, but is a requirement in fully precued CRTs. In a fully cued CRT task a precue provides the subject with full advance information about the particular response required on that trial that allows its selection and preprogramming prior to the presentation of the imperative stimulus. The SRT and the fully cued CRT differ on one important factor: stimulus-response variance. In SRT the stimulus and response are the same on every trial therefore the subject can...
preprogramme the same response for every trial. In the fully cued CRT, although full movement information is provided by the precue, the subject must preprogramme a different response for each trial.

There have been studies of RTs in schizophrenia since the 1930s (Straube and Oades, 1992). The most consistent finding is that schizophrenic patients have significantly slower RTs than normal controls (Vinogradov et al., 1998; Wigal et al., 1997; Elkins and Cromwell, 1994; Nestor et al., 1992; Mannuzza et al., 1984). Another consistent finding is the 'cross over effect' (COE), reported as far back as the 1940s (Rodnick and Shakow, 1940). In normal subjects, in a simple RT (SRT) task, if the interval between the warning signal (S1) and imperative stimulus (S2) is short (three seconds or less), responses are initiated faster on trials where the S1-S2 interval is kept constant or blocked rather than presented randomly across trials. This improved performance is believed to be due to the temporal predictability of the imperative stimulus. However, with longer S1-S2 intervals, normal subjects have similar RTs regardless of whether the S1-S2 intervals are random or blocked. Patients with schizophrenia generally show the same RT benefit from temporal predictability when S1-S2 intervals are short. In contrast, when the S1-S2 intervals are longer, patients with schizophrenia have slower RTs for the blocked S1-S2 intervals than for the random S1-S2 intervals. This phenomenon is called the COE.

In the COE the patients with schizophrenia are failing to use the advance information provided by the warning signal about the temporal predictability of the imperative stimulus to speed up the response. Few studies have examined the effect of other types of advance information on RTs in schizophrenia, for example, use of advance movement parameter information contained in a precue that allows volitional
preprogramming of the response before presentation of the imperative stimulus. One exception is the study by Carnahan et al. (1994) who measured RTs in leukotomised and unleukotomised patients with schizophrenia compared to normals. Using a version of Rosenbaum's RT paradigm (Rosenbaum, 1980), the authors measured RT in uncued, partially cued and fully cued four choice RT (CRT) conditions. The two patient groups were slower than the normals across all RT conditions. The authors concluded that “the leukotomised and the unleukotomised patients were able to use this advance information to facilitate the speed of their responses in much the same way as did subjects in a normal control group”.

The type of information provided by a preparatory signal (S1) presented before an imperative stimulus (S2) can vary. Any signal given a short time before an imperative stimulus will serve as a warning to the subject, allowing them to increase their level of alertness and readiness to respond. This facilitation appears to be optimal with a preparatory interval of 200 ms (Boff and Lincoln, 1988). Alternatively, the preparatory signal may provide advance information about the nature of the response itself, e.g. it may inform the subject that he has to move to the upper key with his right hand when the imperative stimulus is presented. In this case it may be referred to as a ‘movement parameter precue’. This information potentially allows the subject to preselect and preprogramme a specific response from a number of alternatives, provided there is adequate time between the precue and the imperative stimulus to take action. The amount of reduction of RT by ‘warning stimulus’ and ‘movement parameter’ precues also depends on when they are presented relative to the imperative stimulus. Therefore, the interval between the warning signal/precue and the go signal is important in determining the RT facilitation.
The aim of this study is to examine the effects of different types of advance information on RT in schizophrenia (i) invariance of the stimulus and response in SRT relative to uncued CRT (ii) full advance movement parameter information in a precued CRT task. We were also interested in determining if the interval between the warning stimulus / precue (S1) and the imperative stimulus (S2) had similar or differential effects on motor preparation in schizophrenic and normal subjects.

2.2 Methods

2.2.1 Design
A mixed between groups and within subjects design was used. The two groups of subjects, patients with schizophrenia or healthy normals, performed a series of reaction time (RT) conditions: simple reaction time (SRT), uncued four choice RT (CRT), fully cued CRT, and retest of SRT. In each RT condition, an S1-S2 paradigm was used. For each condition, trials were either unwarned (S1-S2 interval of 0 ms) or the imperative stimulus followed the warning signal / precue, with S1-S2 intervals of 200, 800, 1600 or 3200 ms.

2.2.2 Subjects
The characteristics of the two samples are presented in Table 2.1. Ten subjects clinically diagnosed with schizophrenia according to the DSM III R were tested. Each was seen as an out-patient at the National Hospital for Neurology and Neurosurgery. Each patient was rated on the Krawieka Manchester Scale, a 4-point standardised psychiatric assessment scale (Krawieka et al., 1977) for current positive symptoms and negative signs. Overall, the patients were chronically ill and their symptoms were not very severe. Thirteen healthy normals with no previous history of psychiatric or neurological illness, head injury, or drug abuse were tested. The Mini Mental State Examination
(Folstein et al., 1975) was administered to all subjects and no-one scored below the cutoff of 25, indicative of cognitive deficit.

Table 2.1. Details of Subject Groups.

<table>
<thead>
<tr>
<th></th>
<th>Patients with schizophrenia</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
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<td>8</td>
</tr>
<tr>
<td>Female</td>
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<td>5</td>
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<tr>
<td><strong>Hand</strong></td>
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<td></td>
</tr>
<tr>
<td>Right</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Left</td>
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<td>0</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>37.9 (8.0)</td>
<td>38.9 (10.1)</td>
</tr>
<tr>
<td><strong>Mini Mental scores</strong></td>
<td>28.0 (2.5)</td>
<td>29.9 (0.6)</td>
</tr>
<tr>
<td><strong>Duration of illness (years)</strong></td>
<td>13.1 (7.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Krawiecka scale (1977)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms (range 0 - 8)</td>
<td>2.0 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Negative symptoms (range 0 - 5)</td>
<td>2.1 (1.6)</td>
<td></td>
</tr>
</tbody>
</table>

**Daily dosage (sd)** (n)

**Neuroleptics**

|                        |                             |          |
| Chlorpromazine equivalent | 372.5 mg (151.8)           | (8)      |

**Anticholinergics**

|                        |                             |          |
| Disipal equivalent     | 150.0 mg (0.0)              | (2)      |

No medication

(2)
2.2.3 Procedure-reaction time tasks

Responses were made on a response box with six buttons. The two centre black buttons acted as the 'home' keys. Four inches above and 4 inches below each black button were the response buttons. Stimuli were presented on a 14 inch computer screen. A variation of Rosenbaum's (1980) movement precueing RT was used. The subject pressed down the two home keys to begin the trial and a fixation point appeared. The warning stimulus appeared after a variable delay of 1-4 seconds. The imperative stimulus (S2) appeared after the S1-S2 interval (200, 800, 1600 or 3200 ms). On unwarned trials (S1-S2 interval of 0 ms) there was no warning stimulus.

Three types of error trials were recorded: anticipations (RT less than or equal to 100 ms), long responses (RT greater than 3 s), decision errors (incorrect responses in CRT). RT and movement time (MT) from these trials were omitted, and the trials were repeated, that is, trials on which errors occurred were omitted from calculation of mean RTs, but to ensure equal number of trials across subjects any trials with errors were 'replaced' by administering an additional trial. RT was measured (in ms) as the time between the presentation of the imperative stimulus and the release of the home key. MT was measured (in ms) as the time between releasing the home key and pressing the response key. The mean RT for each condition for each subject were used in the analyses.

2.2.3.1 Simple Reaction Time (SRT)

The stimulus and the response were constant across trials within a block. The subject moved from one home key to one response key, and all other keys were covered. Each subject performed two blocks of 50 trials (10 trials per interval), one block with each hand. The order of testing the left or right hand was counterbalanced across subjects in
each group, that is, in the groups of patients with schizophrenia half of the subjects performed the test with their right hand first and half used their left hand first. Similarly, within the group of normals the order of left and right hands was counterbalanced. At the end of the experiment, the SRT condition was presented again to assess possible fatigue or practice effects. Within a block of 50 trials, S1-S2 intervals of 0, 200, 800, 1600 and 3200 ms were randomly presented, 10 trials each.

2.2.3.2 Four Choice Reaction Time (CRT)
There were two movement parameters, hand (right or left) and direction (up or down). The two conditions were either uncued or fully cued. In each condition there were 75 trials with 15 trials of each of the 5 S1-S2 intervals randomly mixed in a block. A similar and randomly mixed number of right and left hand responses were incorporated.

2.2.3.3 Uncued CRT
The warning stimulus consisted of four empty squares appearing to the left and right and above and below the fixation cross. After the S1-S2 interval one square filled which became the imperative stimulus.

2.2.3.4 Fully Cued CRT
One empty square appeared in one of the four possible locations above or below, to the left or right of the fixation point. After the S1-S2 interval the square filled to become the imperative stimulus. Thus the subject knew the precise nature of the required response prior to the presentation of the imperative stimulus.

2.2.4 Order of Testing
The SRT condition was performed first followed by the CRT conditions. The order of performance of the CRT conditions was counterbalanced across subjects in each group.
We considered counterbalancing more appropriate than randomising because for theoretical reasons we wanted subjects to perform SRT prior to the CRT tasks so as not to influence the S-R invariance of SRT by prior exposure to CRT with multiple stimuli and responses. Subsequently, we counterbalanced the order of testing of the CRT tasks.

2.2.5 Statistical Analysis
Mean RTs were used for further analysis. The data were analysed using the Statistical Program for Social Sciences (SPSS), version 8.0. Differences between RTs for the left vs right hand were examined using repeated-measures analysis of variance (ANOVA) with Group as the between subjects factor and Hand (left, right), Condition (SRT, uncued CRT, fully cued CRT), and S1-S2 Interval (0, 200, 800, 1600, 3200ms) as the within subject factors. For both groups, although RTs for the right hand were (non-significantly) faster than those for the left hand, there were no interaction effects of hand with any other variable (Group, Condition, S1-S2 interval). The data for the left and right hands were averaged for each condition. This average was used in all subsequent analyses.

T-tests were used to further investigate significant interactions in the ANOVAs. When t-tests were used equal variances were not assumed. Paired t-tests were used to examine within subject measures and independent t-tests were used for between group measures.

To compare the difference between the ‘true’ SRT and CRT conditions, data from the trials with an S1-S2 interval of 0 ms, i.e., without a warning signal, were analysed using a repeated-measures ANOVA. The between subject factor was Group (patients, controls) and the within subject factors was Condition [SRT (0 ms S1-S2 interval), uncued CRT(0 ms S1-S2 interval)].
In order to examine the effects of advance movement parameter information on CRT, the differences between the uncued and fully cued CRT were examined using a repeated-measures ANOVA. The between subject factor was Group (patients, controls). The within subject factors were Condition (uncued CRT, fully cued CRT), and Interval (200, 800, 1600, 3200 ms).

The effects of using two types of advance information on RT were examined by directly comparing SRTs which can involve volitional and optional use of advance knowledge about S-R invariance for preprogramming of the response prior to stimulus presentation, and the fully cued CRT where the precue provides full information about the specific response required on that trial which allows its selection and preparation before presentation of the imperative stimulus. A repeated-measures ANOVA was used with Group (patients, controls) as the between subject factor and Condition (SRT, fully cued CRT), and Interval (200, 800, 1600, 3200 ms) as the within subject factors.

Movement time was analysed using a repeated-measures ANOVA. The between subject factor was Group (patients, controls) and the within subject factors were Condition (SRT, uncued CRT, fully cued CRT) and Interval (0, 200, 800, 1600, 3200 ms).

Error data were analysed using Mann Whitney U tests for the between groups comparisons and Wilcoxon matched pairs test for the within subject analyses.

2.3 Results

The two groups did not differ in age ($t = 0.25$, d.f. = 21 $p = 0.80$) or male to female ratio ($x^2 = 0.25$ d.f. = 1, $p = 0.62$). Although the groups differed on scores on the Mini
Mental Examination ($t = 2.5$ d.f. = 21, $p = 0.05$), no subject scored below the cutoff of 25.

Fatigue or practice effects were assessed by comparing SRTs performed at the beginning and end of the session. The controls had a mean RT of 351 ms ($SD = 57$ ms) for the first SRT and a mean RT of 373 ms ($SD = 63$ ms) for the final SRT, a mean difference of 22 ms ($SD = 33$ ms). The patients with schizophrenia' mean RT was 442 ms ($SD = 105$ ms) for the first SRT and 474 ms ($SD = 104$ ms) for the final SRT, a mean difference of 17 ms ($SD = 21$ ms). There was no significant difference between the change in RT between the two groups ($t = 0.41$ d.f. = 20, $p = 0.69$).

2.3.1 Error Data

Very few errors of any type were made by the patients or normals. In the SRT, for the patients with schizophrenia, the median number of anticipation errors was 0.10 (range 0.00 - 0.80) and the median number of long responses was 0.00 (range 0.00 - 0.10). For the controls, for SRT, the median number of anticipation errors was 0.10 (range 0.00 - 0.40), the median number of long responses was 0.00 (range 0.00 - 0.20). Across the CRT conditions, the patients with schizophrenia had a median of 0.10 (range 0.00 - 3.50) anticipation errors, 0.00 (range 0.00 - 0.30) long responses and 0.10 (range 0.00-0.10) decision errors. Across the CRT conditions, the controls had a median of 0.01 (range 0.00 - 0.20) anticipation errors, 0.00 (range 0.00 - 0.15) long responses and 0.00 (range 0.00- 0.20) decision errors.

A series of Mann-Whitney U tests revealed that there were no significant differences between the patients and controls in the number of anticipations, decision errors, or long responses in the various RT conditions ($p > 0.05$). Similarly, Wilcoxon matched pairs tests showed that there were no differences in errors between the various RT conditions...
for the patients with schizophrenia (p > 0.05). For the controls, there were more
anticipation errors in the SRT compared to the uncued CRT (Z = 2.5, p = 0.01) but not
in the fully cued CRT (Z = 1.21, p = 0.22) conditions for the controls. Also, for the
controls there were more anticipation errors in the fully cued CRT than in the uncued
CRT (Z = 2.6 p = 0.01).

2.3.2 Unwarned SRT vs Unwarned and Uncued CRT
The mean RTs for the two groups in unwarned SRT and unwarned and uncued CRT
conditions are presented in Figure 2.1. The Group effect was significant [F(1,20) = 7.94
p = 0.01] with patients with schizophrenia having slower reaction times than the
controls. The Condition effect was significant [F(1,20) = 18.16, p = 0.001] with SRTs
being faster than CRTs, however the Group x Condition interaction was not significant
(p > 0.1). In order to determine if the speeding up of SRT relative to CRT which is an
index of preprogramming was equivalent in the two groups, the differences in RT
between the two conditions were examined using paired t-tests for each group. The
mean differences between the CRT and SRT conditions was 60.3 ms (SD = 50.6) for the
controls and 69.1 ms (SD = 91.8) for the patients with schizophrenia. The unwarned
SRT was significantly faster than the uncued and unwarned CRT for both the controls (t
= 4.30, d.f. = 12, p = 0.01) and the patients with schizophrenia (t = 2.30, d.f. = 8, p =
0.05).

2.3.3 Uncued CRT vs Fully cued CRT
The mean RTs for the two groups for the uncued and fully cued CRT are presented in
Figure 2.2. The main effects of Group [F(1,21) = 8.32 p = 0.01], Condition [F(1, 63)
=69.92 p = 0.001], and Interval [F(3,63) = 13.23 p = 0.001] were significant. The
Group x Condition interaction was not significant (p < 0.05). In contrast, the Condition
x Interval [F(3,63) = 5.18 p = 0.003], the Group x Interval [F(3,63) = 4.84 p = 0.004]

and the Group x Condition x Interval \([F(3, 63) = 4.29, p = 0.01]\) interactions were significant.

Further analysis of the Condition effect revealed that across the two groups and the various intervals, the uncued CRT was significantly slower than the fully cued condition \((p = 0.001)\). The significant main effect of Interval was also examined in more detail. Across the two groups, RTs for the 800 ms S1-S2 interval were slower than those for the 200 ms \((p = 0.01)\), the 1600 ms \((p = 0.001)\) and the 3200 ms \((p = 0.001)\) intervals. No other intervals differed significantly.

Further analysis of the Group x Interval interaction revealed that for the control subjects RTs for the 3200 ms intervals were faster than those for the 200 ms \((p = 0.04)\) and the 800 ms interval \((p = 0.002)\). In contrast, for the patients with schizophrenia RTs for the 800 ms interval were slower than those for the 200, 1600 and 3200 ms intervals \((p < 0.01)\) and no other intervals differed \((p > 0.05)\).

Further analysis of the Group x Condition x Interval interaction revealed that across the two CRT tasks for the controls subjects fully cued CRT were significantly faster than the uncued CRT at each interval \((200, 800, 1600, 3200\) ms) \((p < 0.02)\). On average for the normals, the fully cued CRT was faster than the uncued CRT by 19.9, 83.1, 68.7 and 73.4 ms respectively with the 200, 800, 1600 and 3200 ms S1-S2 intervals. Thus the differences between the two CRT conditions at the 200 ms interval although small \((\text{mean} = 19.9\) ms, \(\text{SD} = 24.5)\) reached statistical significance. For the patients with schizophrenia the RTs for the fully cued CRT were significantly faster than the CRTs for the uncued CRT for the 1600 ms (faster on average by 86 ms) and 3200 ms (faster on average by 77.4 ms) intervals \((p < 0.01)\) only.
Figure 2.1 Mean reaction time for the normal subjects and the patients with schizophrenia in the unwarned simple reaction time task (SRT) (black bar) and the uncued and unwarned choice reaction time (CRT) (white bar) tasks.
Figure 2.2 Mean reaction times for the normal controls and the patients with schizophrenia in the uncued (circle) and fully cued (square) CRT conditions.
Figure 2.3 Mean reaction times for the normal controls and the patients with schizophrenia in SRT (triangle) and fully cued CRT (square) conditions.
2.3.4 SRT vs Fully Cued CRT

The mean RTs for the two groups for the SRT and fully cued CRT are shown in Figure 2.3. The main effects of Group \([F(1,20) = 7.60 \ p = 0.01]\), Condition \([F(1, 20) = 12.19 \ p = 0.002]\) and Interval \([F(3,60) = 11.89 \ p = 0.001]\) were significant. The Group x Condition interaction \([F(1,20)= 2.35, \ p=0.14]\) was not significant. The Condition x Interval \([F(3, 60) = 2.80, \ p = 0.05]\), Group x Interval \([F(3,60) = 3.43 \ p = 0.02]\), and the Group x Condition x Interval \([F(3,60) = 9.52 \ p = 0.01]\) interactions were significant.

The significant three way interaction was examined further by investigating differences between SRT and fully-cued CRT for each of the four intervals within each group. For the normal subjects, fully cued CRTs were significantly slower than SRTs at the 200 ms interval \((p=0.001)\) but not at the 800, 1600, or 3200 ms intervals \((p > 0.1)\). In contrast, for the patients with schizophrenia, CRTs were significantly slower than SRTs for the 800 \((p = 0.01)\) and the 3200 ms interval \((p = 0.04)\) but not for the 200, or the 1600 ms S1 - S2 intervals \((p > 0.1)\).

2.3.5 Movement Time

The main effects of Group \([F(1,20) =8.29 \ p = 0.01]\), Condition \([F(2,31) = 10.67 \ p = \ 0.001]\) were significant, but not the main effect of Interval \([F(3,54) = 1.94 \ p = 0.14]\). There were no significant interaction effects \((p > 0.05)\). The patients with schizophrenia had slower MTs \((278 \text{ ms, SD = 68 ms})\) than the controls \((190 \text{ ms, SD = 73})\). MTs were significantly faster in the SRT condition compared to each CRT condition \((p < 0.05)\). The two CRT conditions did not differ.

2.3.6 Correlational Analysis

Pearson's correlations were used to examine the relationship between the individual symptoms of schizophrenia as rated on the Krawieka Manchester Scale, depression as
rated on the Beck Depression Inventory and reaction times, movement times and errors.

For each condition the reaction times (RT) and movement times (MT) for each interstimulus interval (ISI) and the mean for each condition were used, for example, Fully Cued CRT ISI interval 0, 200, 800, 1600 and 3200ms were used separately and also the mean RT for Fully Cued CRT condition. The results are presented in Table 2.2.

The p values were adjusted for the number of correlations (250) by carrying out a Bonferroni correction. After this adjustment there were no significant correlations remaining.

There is a possibility that factors such as levels of antipsychotic medication, depression, or cognitive deficits, which have been shown to differ among patients with schizophrenia, could confound the findings of correlational analyses. Therefore, Pearson’s Partial Correlations were run controlling for dose of neuroleptic, BDI score, and the Mini Mental scores. These results are presented in Table 2.3. After carrying out Bonferroni corrections for the number of correlations (225) there were no significant correlations.
Table 2.2 Pearson's correlations between reaction time, movement time, errors and the individual symptom ratings of the Krawieka Manchester Scale and Depression as rated on the Beck Depression Inventory (BDI). Only coefficients of $p < 0.05$ are presented. CRT = choice reaction time, ISI = inter stimulus interval, MT = movement time, SRT = Simple reaction time.

<table>
<thead>
<tr>
<th></th>
<th>Krawieka Depression</th>
<th>Flattened Affect</th>
<th>Poverty of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncued CRT 3200 ms</td>
<td>$r = -0.64$</td>
<td>$r = -0.71$</td>
<td></td>
</tr>
<tr>
<td>ISI</td>
<td>$p &lt; 0.05$</td>
<td>$p = 0.02$</td>
<td></td>
</tr>
<tr>
<td>Fully Cued CRT 1600 ms ISI</td>
<td>$r = -0.67$</td>
<td>$p = 0.04$</td>
<td></td>
</tr>
<tr>
<td>MT SRT</td>
<td>$r = 0.68$</td>
<td>$r = 0.56$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.05$</td>
<td>$p &lt; 0.01$</td>
<td></td>
</tr>
<tr>
<td>MT Uncued CRT</td>
<td>$r = 0.67$</td>
<td>$r = 0.60$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = 0.03$</td>
<td>$p &lt; 0.01$</td>
<td></td>
</tr>
<tr>
<td>MT Fully Cued CRT</td>
<td></td>
<td></td>
<td>$r = 0.63$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$p &lt; 0.01$</td>
</tr>
<tr>
<td>CRT Anticipation</td>
<td></td>
<td></td>
<td>$r = 0.68$</td>
</tr>
<tr>
<td>Errors</td>
<td></td>
<td></td>
<td>$p = 0.03$</td>
</tr>
</tbody>
</table>
Table 2.3 Pearson's Partial correlations between reaction time, movement time, errors and the individual symptom ratings of the Krawieka Manchester Scale controlling for medication, level of depression and Mini Mental score. Only coefficients of p < 0.05 are presented. CRT = choice reaction time, ISI= inter stimulus interval, SRT = Simple reaction time.

<table>
<thead>
<tr>
<th></th>
<th>Krawieka Flattened Affect</th>
<th>Psychomotor Retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully Cued CRT 800 ms ISI</td>
<td>r = -0.87 d.f. = 3</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fully Cued CRT 1600 ms ISI</td>
<td>r = -0.88 d.f. = 3</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
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<tr>
<td>SRT 800 ms ISI</td>
<td>r = -0.91 d.f. = 3</td>
<td>p = 0.03</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>SRT 1600 ms ISI</td>
<td>r = -0.99 d.f. = 3</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CRT Anticipation errors</td>
<td>r = 0.95 d.f. = 3</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CRT Long Response Errors</td>
<td>r = 0.9 d.f. = 3</td>
<td>r = 0.94 d.f. = 3</td>
</tr>
<tr>
<td></td>
<td>p = 0.02</td>
<td>p = 0.02</td>
</tr>
</tbody>
</table>

2.4 Discussion

Overall, the RTs and MTs of patients with schizophrenia were significantly slower and more variable than those of age-matched normals across all conditions. Unwarned SRT were significantly faster than the uncued CRT in both groups. For both groups the fully cued CRTs were significantly faster than the uncued CRTs. There was a curious interval effect for the patients with schizophrenia which resulted from the fact that in the fully cued CRT condition, the patients with schizophrenia had CRTs which were
significantly faster at the 200 ms than the 800 ms interval. Besides significant slowness in movement initiation and execution, significant differences in interval effects were the main factor that distinguished the various RTs of the patients and controls.

Before we discuss the main results further we will consider and exclude the possible effects of a number of confounding factors on the RT results. As it was not possible to test the patients with schizophrenia off medication, there is always the possibility that the results obtained are affected by the medication that 8 of the 10 patients were taking. Most existing studies have found no effect of neuroleptic medication on RTs (Heilizer, 1959; Pearl, 1962; Pugh, 1968; Held et al., 1970; Vrtunski et al., 1989). Nevertheless, in a RT paradigm with auditory stimuli, RTs were significantly lower for schizophrenic patients on medication compared to those patients off medication (Pfefferbaum et al., 1989). While the former results suggest that medication status may not affect RTs, the latter study suggests that the slowing of RTs in schizophrenia may be partly attributable to the neuroleptic medication that is taken by most patients. If this is the case, then RTs should be assessed in drug-free patients, a procedure which is not feasible in most studies for clinical reasons. In the present study, there was some indication that the RTs of the two patients who were not taking any medication at the time of the study were in fact somewhat slower than those of the remaining 8 patients who were on medication.

For both groups, RTs slowed slightly during the experiment as seen by the increased RT in the final SRT task compared to the initial SRT task. As there was no significant difference between the two groups on the amount of slowing, the results are not confounded by different patterns of fatigue effects in the two groups.
Precueing produced no differential effect on MT, as MTs for uncued and fully cued conditions did not differ significantly. In contrast, precueing or provision of advance movement parameter information, produced a significant effect on RTs. RTs were significantly faster for the fully cued than for the uncued CRT. The differential effects of precueing on MTs and RTs suggests that the use of advance information for motor preparation is complete by the end of the RT period when the subject lifts his or her index finger from the home key and that there is no evidence of 'on line' preparation during movement execution.

The two groups did not differ in the number of anticipations, decision errors, or long responses. Therefore the differences in RT between the patients with schizophrenia and normals do not appear to be associated with different speed-accuracy trade offs across the two groups.

2.4.1 Use of stimulus-response invariance for preprogramming in SRT: SRT vs Uncued CRT
The patients with schizophrenia were significantly slower than the controls on both the SRT and uncued CRT tasks. However, for both groups the SRT was significantly faster than CRT. These results suggest that in the SRT condition, which involves optional and volitional preprogramming, the patients with schizophrenia preprogramme the response prior to presentation of the stimulus. As a result this condition was significantly faster than the uncued and unwarned CRT which is a purely stimulus driven task where no preprogramming is possible and the correct response is selected, prepared and initiated only after presentation of the imperative stimulus. The significant slowness of SRT in schizophrenia relative to normals agrees with the results of previous studies (Huston et al., 1937; White et al., 1987; Schwartz et al., 1989). Nuechterlein (1977) has reviewed the few studies which have directly compared SRT and uncued CRT in schizophrenia.
Similar to the present results, all previous studies have found that CRT is slower than SRT for patients with schizophrenia similar to normals. However, the present results also showed that the CRT-SRT difference was similar in the two groups.

2.4.2 Use of advance movement parameter information for preprogramming in CRT: Fully precued v uncued CRT or SRT

The fully cued CRTs were significantly faster than the uncued CRTs for the patients with schizophrenia similar to the normals. This is in agreement with previous studies suggesting that valid cues are used by patients with schizophrenia to speed up RT (Nestor et al., 1992; Posner et al., 1988). However, the significant Group x Interval and Group x Condition x Interval interactions when comparing the fully cued CRT with the uncued CRT or SRT, revealed that the patients with schizophrenia showed anomalies in the use of advance information. Replicating previous findings (Jahanshahi et al., 1992) for the normal subjects with the RT tasks used, an S1-S2 interval of 200 ms is not long enough for subjects to use advance information to speed up fully cued CRTs to the level of SRTs. But with S1-S2 intervals of 800 ms or longer, the advance information provided by the precue is fully used by normal subjects to speed up precued CRTs and make these equivalent to the corresponding SRTs. For the patients with schizophrenia an unusual S1-S2 interval effect was present, mainly due to slower fully cued CRTs for the 800 ms and faster fully precued CRTs for the 200 ms S1-S2 interval. As a result, in contrast to the normals, fully precued CRTs were equivalent to SRT even for the 200 ms interval, but not for the longer 800 ms S1-S2 interval or the 3200 ms interval. Examination of the raw data shows that the observed interval effect was not caused by a single outlier. Nine of the ten patients had slower fully cued CRTs for the 800 ms S1-S2 interval relative to the 200 ms S1-S2 interval. This 'abnormal' S1-S2 interval effect may reflect inconsistencies of 'set' in patients with schizophrenia similar to that seen in the 'cross over effect' (Shakow, 1962). One possible explanation of the increased RTs
for an 800 ms interval for the patients with schizophrenia is that conscious processing interfering with externally-cued RT processes. There is evidence of a delay between motor response and conscious awareness (Libet et al., 1983; Libet, 1985; Castiello et al., 1991). Libet et al. (1983; Libet, 1985) report that the readiness potential, a negative cortical potential related to voluntary movement preparation (Kornhuber and Deeke, 1965), occurred about 400 ms before subjects signalled conscious awareness of their decision to move. Castiello et al. (1991) report that a corrected motor response to a target which shifted position after movement onset occurred, on average, 315ms prior to a vocal response signalling awareness of the target shift. The patients with schizophrenia may be experiencing interference from the conscious awareness of the target and movement strategy in the 800 ms S1-S2 interval that is not present in the 200 ms interval.

There are some similarities between the current results for patients with schizophrenia and results from patients with Parkinson’s disease in a similar study (Jahanshahi et al., 1992). Both patient groups had significantly slower RTs and MTs than age-matched normals, both were able to use the S-R invariance to preprogramme the response in SRT and use advance information in precued CRT tasks to speed up their RTs relative to uncued CRT. However, both groups showed ‘abnormal’ interval effects. Patients with Parkinson’s disease required a longer S1-S2 interval (3200 ms) to speed up fully cued CRTs to the level of SRT whereas elderly normals did so with an S1-S2 interval of 800 ms (Jahanshahi et al., 1992). In the present study, instability of attentional set in schizophrenia was associated with equivalent RTs for the fully cued CRT and SRT for the 200 ms and 1600 ms S1- S2 interval but not the 800 or 3200 ms S1-S2 intervals.
2.4.3 Deficits in volitional processes in schizophrenia

The extent to which actions are volitional or reflexive differ on a continuum from the completely automatic and reflexive such as the knee jerk, to the fully internally-driven such as spontaneous actions. Most of our daily actions rest somewhere in between. This is also true of the various RT tasks used in the present study, which differed in the degree of volitional control required for selection, preparation and initiation of a response. The uncued CRT task was probably the least demanding of volitional control. For this reason, the patients with schizophrenia showed no significant differences in uncued CRTs relative to the normal subjects. The SRT task would probably be placed next on a continuum of degree of volitional control required. The optional but internally driven preprogramming in the SRT task is dependent on an act of “will”, but as the stimulus-response pairing never varies, the subject preprograms the same response on each trial. There was evidence that the patients with schizophrenia were engaging in this. Finally, in the fully precued CRT, since the imperative stimulus repeated the information held in the precue, preprogramming was also optional and volitional and the subject could simply wait for the imperative stimulus before programming the response similar to uncued CRT. However, in the fully cued CRT although the exact response is known prior to presentation of the imperative stimulus, the subject must preprogramme a *different* response for each trial. Thus a higher degree of volitional control is required relative to SRT, where given the S-R invariance, the same response is preprogrammed across trials in a block.

Performance of SRT tasks concurrently with a second attention-demanding task under dual task conditions, which introduces a capacity load and requires greater volitional control, has been shown to be particularly detrimental to the performance of patients with schizophrenia (Schwartz et al., 1989). In general, evidence suggests that patients with schizophrenia are particularly slowed by increases in task complexity in CRT tasks.
(Slade, 1971; Yates and Korboot, 1970; Marshall, 1973; Hemsley, 1976a; Williams and Hemsley, 1986). For example, in a review of the literature on information processing in schizophrenia, Hemsley (1976b) concluded that CRT tasks involving low S-R compatibility are more sensitive to deficits in schizophrenia (Slade, 1971; Venables, 1958). There is some suggestion from the present results that in schizophrenia RT deficits become more evident as tasks require greater volitional control. As noted above, compared to SRT where the same response is preprogrammed across all trials, in fully cued CRT, a different response has to be preprogrammed on each trial, hence requiring greater allocation of attention and volitional control. It was precisely on the fully cued CRT condition that the patients with schizophrenia showed unusual and inconsistent interval effects suggesting instability of attentional set. These unusual interval effects are reminiscent of the 'cross over effect' which has been replicated in schizophrenia in numerous studies. The cross over effect has also been interpreted as reflecting an impaired ability to maintain attentional set (Shakow, 1962). Such instability of attentional set may contribute to other deficits observed in schizophrenia such as increased perseveration on the Wisconsin Card Sorting Test (Weinberger et al., 1986) or the 'modality shift' effect (Zubin, 1975).

Therefore, the present results suggest that ordinarily, the patients with schizophrenia do not have any major deficits in preprogramming of responses in an SRT or fully cued CRT task. However, in the latter task, where the volitional demands of preprogramming are higher since a different response has to be prepared on each trial, patients show some unusual and inconsistent interval effects suggesting instability of attentional set. In the present study, it was not possible to differentiate subgroups of patients with predominance of negative signs or positive symptoms. It is possible that future studies using RT tasks requiring greater volitional control (for example, with high
stimulus-response incompatibility requiring volitional S-R decoding prior to response selection) and a sample of patients with schizophrenia and predominance of negative signs may reveal greater deficits in willed action.
CHAPTER 3

Study 2: Concurrent Performance of Motor Tasks and Processing Capacity in Patients with Schizophrenia

3.1 Introduction

It has been suggested that as cognitive load increases, patients with schizophrenia show greater task impairment than normals signifying resource limitations in this disorder (Nuechterlein and Dawson, 1984). One way to test the effects of increasing cognitive load is to compare performance on dual task compared to single task conditions (Norman and Bobrow, 1975). Any task is carried out more successfully if we allocate our undivided attention to it. As demands on attentional capacity increase, for example in concurrent or dual task conditions, performance on attended tasks becomes more impaired (Wickens, 1984). The degree to which a task is impaired, however, depends on the amount of attentional capacity it demands. An automatic task would not interfere with a more demanding task but there would be interference of one very demanding task upon another (Heur and Wing, 1984). It would be expected that the degree of performance decrement in a dual task compared to a single task condition would be greater in patients with schizophrenia than in controls, due to the patients limited resources and hence inability to adequately handle the increased cognitive load. There is evidence that under dual task conditions patients with schizophrenia are differentially more impaired than normals (Granholm et al., 1996) and other psychiatric patients (Schwartz et al., 1989; Schwartz et al., 1991). These studies (Granholm et al., 1996; Schwartz et al., 1989; Schwartz et al., 1991) used a simple reaction time task and tests of cognitive skill, such as a visual search task or counting.
Another way to investigate attentional processing capacity in schizophrenia is to assess concurrent performance of motor tasks such as finger tapping and peg placement which differ in terms of their attentional demands. Peg placement as in the Purdue Pegboard task involves sequential movements such as grasping and picking a peg up, followed by its transport and insertion into the holes on the pegboard. Because of its visually driven nature, performance on the pegboard appears to gain prominence over repetitive index finger tapping, which can be performed in a more automatic fashion. As a result, in normals when performed concurrently, finger tapping interferes relatively less with peg placement, whereas concurrent peg placement affects finger tapping more (Brown and Jahanshahi, 1998).

The aim of this study was to examine processing resources in schizophrenia by comparing the performance of two motor tasks, tapping and pegboard placement, under unimanual, bimanual and dual task conditions in patients with schizophrenia and normal controls.

3.2 Method

3.2.1 Subjects
Eleven (2 female, 9 male) subjects with a clinical diagnosis of schizophrenia according to the DSM IIIR criteria were tested. Each was seen as an outpatient at the National Hospital for Neurology and Neurosurgery. Each patient was rated on the Krawieka Manchester Scale (Krawieka et al., 1977), a 4- point standardised psychiatric assessment scale for current positive and negative symptoms. The mean score for positive symptoms (incoherence, delusions and hallucinations) was 2.0 and the mean score for negative signs (poverty of speech, flattened affect and psychomotor retardation) was 2.2. The mean age for the patients was 38.5 (range 27 - 55). As a
group, the patients with schizophrenia were chronically ill, with a mean duration of illness of 14.2 years (SD = 7.4). All patients except two were on medication with nine on neuroleptics (mean dose = 375.6 mg, SD = 142.3). Thirteen (5 female, 8 male) healthy normals with no previous history of psychiatric or neurological illness, head injury, or drug abuse were tested. Their mean age was 38.15 (range 21 - 62). All subjects were right handed. To screen for cognitive deficits, the Mini Mental State Examination (Folstein et al., 1975) was administered to all subjects. None of the subjects scored below the cut-off indicative of cognitive deficit.

3.2.2 Procedure
All subjects performed finger tapping and the Purdue Pegboard under unimanual, bimanual and dual task conditions. On the Purdue Pegboard, subjects were required to place metal pegs (3mm x 25 mm) in a vertical row of holes, as quickly as possible for a 30 s period. Subjects performed the task with each hand separately and then bimanually. The measures of unimanual and bimanual performance were the mean number of pegs placed with the left and right hands under each condition.

The second task was repetitive index finger tapping. Subjects were required to continuously tap a 25 mm button as quickly as possible for a 30 s period. The button activated a 150 g standard microswitch. The task was performed with each hand separately and bimanually. As with the pegboard, the measures of unimanual and bimanual performance were the mean number of taps with the left and right hands under each condition.

Subjects also performed a combined bimanual task. This involved tapping with one hand and placing pegs with the other. The test was performed twice, once with each hand-task combination each time for 30 s. The average of the two tests was calculated
for each task. For all conditions the measures of bimanual performance are expressed as percentages of unimanual performance [e.g. \((\text{PEG}_b/\text{PEG}_u) \times 100\)]. In the combined task condition, subjects were instructed to perform both tasks at the same time as fast as they could and not to concentrate on one to the exclusion of the other.

The order of testing was randomised across subjects. All subjects were assessed on the Beck Depression Inventory (BDI; Beck et al., 1961).

### 3.3 Results

The mean ages of the two groups did not differ significantly \([F(1, 23) = 0.032, p = 0.87]\). The mean of the MMS scores for the patients was 28.2 (SD = 2.5) and for the controls 29.9 (SD = 0.3). The difference between the two groups was significant \([F(1,23) = 6.35, = 0.02]\). The mean score on the BDI for the patients was 14.4 (SD = 10.3) and for the controls was 4.5 (SD = 5.1), a difference which was significant \([F(1, 22) = 9.20, p < 0.01]\). The group differences in task performance were analysed both with and without MMS and BDI scores as covariates.

Table 3.1 shows the mean performance of the two groups for each of the test conditions, as well as the performance of the bimanual conditions as a percentage of unimanual task performance. Also shown are the results of the one way analyses of variance and covariance.

For the pegboard, the patients with schizophrenia had significantly slower performance than the controls for the unimanual and bimanual tasks. The number of pegs placed in the bimanual condition as a percentage of the unimanual condition did not differ
Table 3.1. Performance of the two groups on the tapping and Purdue pegboard tasks (mean and standard deviation) under unimanual, bimanual, and dual task conditions.

<table>
<thead>
<tr>
<th></th>
<th>Patients with schizophrenia</th>
<th>Normal Controls</th>
<th>p</th>
<th>*p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegboard unimanual</td>
<td>13.1 (2.3)</td>
<td>16.3 (1.8)</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pegboard bimanual</td>
<td>11.3 (2.8)</td>
<td>14.1 (1.7)</td>
<td>&lt;0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>% of unimanual pegboard</td>
<td>85.4 (10.1)</td>
<td>87.2 (7.6)</td>
<td>0.53</td>
<td>0.74</td>
</tr>
<tr>
<td>Tapping unimanual</td>
<td>145.5 (40.0)</td>
<td>172.6 (19.1)</td>
<td>0.06</td>
<td>0.19</td>
</tr>
<tr>
<td>Tapping bimanual</td>
<td>132.8 (38.7)</td>
<td>165.2 (26.4)</td>
<td>&lt;0.03</td>
<td>0.26</td>
</tr>
<tr>
<td>% of unimanual tapping</td>
<td>92.7 (15.0)</td>
<td>94.2 (9.8)</td>
<td>0.77</td>
<td>0.55</td>
</tr>
<tr>
<td>Pegboard with tapping</td>
<td>13.3 (2.5)</td>
<td>15.0 (2.1)</td>
<td>&lt;0.04</td>
<td>0.30</td>
</tr>
<tr>
<td>% of unimanual pegboard</td>
<td>101.3 (5.2)</td>
<td>92.5 (8.7)</td>
<td>&lt;0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>Tapping with pegboard</td>
<td>100.8 (38.3)</td>
<td>149.6 (22.3)</td>
<td>&lt;0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>% of unimanual tapping</td>
<td>71.2 (22.9)</td>
<td>86.8 (9.8)</td>
<td>0.05</td>
<td>0.26</td>
</tr>
</tbody>
</table>

PEGu – PEGc

% subjects showing improvement  45.5%  15.4%
% subjects showing no change  27.3%  7.7% $X^2(2) = 5.92$  p = 0.05
% subjects showing deterioration  27.3%  76.9%

*Results of one way analysis of covariance with MMS and BDI score as covariate
significantly between the two groups. Similar results were found for the tapping test. While tapping bimanually the patients were significantly slower than the controls and the difference approached significance (p = 0.06) for unimanual tapping. But when bimanual tapping was considered as a percentage of unimanual performance, the two groups did not differ significantly.

Under dual task conditions of concurrent tapping and peg placement an interesting pattern of results emerged. The absolute numbers of pegs and taps were significantly different between the patients and the normals, with the patients having fewer taps and placing fewer pegs in the dual task condition. The patients and controls also differed significantly in terms of percentage of change from the unimanual performance. However, relative to performance of pegboard alone, the patients with schizophrenia showed improved performance on the pegboard under the dual task condition, while the performance of the normals was worse. Also the patients with schizophrenia showed a significantly greater drop in tapping performance under dual task conditions than the normals.

Under dual task conditions, for the pegboard task, we also examined the distribution of the absolute difference (pegs placed in unimanual task – pegs placed in bimanual dual task) for individual subjects in each group. This showed that peg placement in the dual task condition improved in 45%, remained constant in 27% and deteriorated in 27% of the group with schizophrenia, whereas performance on the pegboard under the dual task condition improved in only 15%, remained constant in 8% and deteriorated in 77% of the controls. These proportions were significantly different across the two groups ($X^2 = 5.92$, d.f. = 2, p = 0.05).
When the group differences in MMS and BDI scores were covaried out, only the group differences in the unimanual pegboard remained statistically significant.

3.3.1 Correlational Analysis

Pearson’s correlations were used to examine the relationship between the individual symptoms of schizophrenia as rated on the Krawieka Manchester Scale, depression as rated on the Beck Depression Interval (BDI), and peg placement and tapping speed. The significant results (p < 0.05) are presented in Table 3.2. After carrying out Bonferroni corrections for the number of correlations (130) there were no significant correlations.

There is a possibility that factors such as depression, medication or cognitive deficits could confound the findings of correlational analyses. Therefore, Pearson’s Partial Correlations were run controlling for dose of neuroleptic, BDI score, and Mini Mental score. R and p values are presented in Table 3.3 for the significant results of the Pearson’s Partial Correlations. After carrying out Bonferroni corrections for the number of correlations (117) there was one significant correlation. There was a significant negative correlation between rating of incoherence and the number of pegs placed in the dual task condition ($r = -0.995$, d.f = 3, $p < 0.001$). This means that higher ratings of incoherence were associated with reduced tapping in the dual task condition.
Table 3.2. Pearson's correlations between measures of tapping and peg placement under different conditions and the individual symptom ratings of the Krawieka Manchester Scale and depression as rated on the Beck Depression Inventory (BDI). The r and p values are given. Only coefficients with p < 0.05 are presented

<table>
<thead>
<tr>
<th>Krawieka Scale</th>
<th>Depression</th>
<th>Delusion</th>
<th>Incoherence</th>
<th>Poverty of speech</th>
<th>Flattened affect</th>
<th>BDI</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tap unimanually</td>
<td>r = -0.64</td>
<td>r = -0.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left hand</td>
<td>p &lt; 0.05</td>
<td>p = 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap unimanually</td>
<td>r = -0.74</td>
<td>r = -0.69</td>
<td>r = -0.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right hand</td>
<td>p = 0.02</td>
<td>p = 0.03</td>
<td>p &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap bimanually, left hand</td>
<td>r = -0.79</td>
<td>r = -0.77</td>
<td>r = -0.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap bimanually, right hand</td>
<td>r = -0.71</td>
<td>r = 0.79</td>
<td>r = 0.74 p</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap dual task, left hand</td>
<td>r = -0.76</td>
<td>r = -0.73</td>
<td>r = -0.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap dual task, right hand</td>
<td>r = -0.66</td>
<td>r = -0.64</td>
<td>r = -0.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg unimanually left hand</td>
<td>r = -0.65</td>
<td>r = 0.74 p</td>
<td>r = 0.74 p</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg unimanually right hand</td>
<td>r = 0.04</td>
<td>= 0.02</td>
<td>= 0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg bimanually, left hand</td>
<td>r = -0.64</td>
<td>r = -0.67</td>
<td>r = -0.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg bimanually, right hand</td>
<td>r = -0.76</td>
<td>r = -0.67</td>
<td>r = -0.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg dual task, left hand</td>
<td>r = -0.80</td>
<td>r = -0.73</td>
<td>r = -0.65</td>
<td>r = -0.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg dual task, right hand</td>
<td>r = -0.66</td>
<td>r = -0.67</td>
<td>r = -0.78</td>
<td>r = -0.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg dual task, overall</td>
<td>r = -0.76</td>
<td>r = -0.65</td>
<td>r = -0.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>p &lt; 0.01</td>
<td>p = 0.04</td>
<td>p = 0.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.3 Pearson's partial correlations between measures of tapping and peg placement under different conditions and the individual symptom ratings of the Krawieka Manchester Scale, controlling for medication, level of depression and Mini Mental score. The r and p values are given. Only coefficients with p < 0.05 are presented.

<table>
<thead>
<tr>
<th>Krawieka Scale</th>
<th>Depression</th>
<th>Delusion</th>
<th>Incoherence</th>
<th>Poverty of speech</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tap left hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap right hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap bimanually, left hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap bimanually, right hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap dual task, left hand</td>
<td>r = -0.91 p = 0.03</td>
<td>r = -0.92 p = 0.03</td>
<td>r = -0.89 p = 0.04</td>
<td></td>
</tr>
<tr>
<td>Tap dual task, right hand</td>
<td></td>
<td>r = -0.88 p &lt; 0.05</td>
<td>r = -0.95 p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Tap dual task, overall</td>
<td>r = -0.88 p &lt; 0.05</td>
<td>r = -0.91 p = 0.03</td>
<td>r = -0.93 p = 0.02</td>
<td></td>
</tr>
<tr>
<td>Peg left hand</td>
<td>r = -0.96 p &lt; 0.01</td>
<td>r = -0.96 p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg right hand</td>
<td>r = -0.96 p &lt; 0.01</td>
<td>r = -0.90 p = 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg bimanually, left hand</td>
<td></td>
<td>r = -0.96 p &lt; 0.01</td>
<td>r = -0.94 p = 0.02</td>
<td></td>
</tr>
<tr>
<td>Peg bimanually, right hand</td>
<td></td>
<td>r = -0.96 p &lt; 0.01</td>
<td>r = -0.94 p = 0.02</td>
<td></td>
</tr>
<tr>
<td>Peg dual task, left hand</td>
<td>r = -0.98 p &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg dual task, right hand</td>
<td>r = -0.97 p &lt; 0.01</td>
<td>r = -0.96 p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg dual task, overall</td>
<td>r = -0.99 p &lt; 0.001</td>
<td>r = -0.92 p = 0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.4 Discussion

The results show that patients with schizophrenia were significantly slower than the normal controls— they placed fewer pegs and had reduced tapping speed in unimanual and bimanual conditions. However, despite this overall slowness, the decrement in bimanual performance as a percentage of unimanual performance was not significantly different for the patients and controls on either the pegboard or tapping tasks. This suggests that although motor abnormalities such as poverty of action, perseverative movements (Manschreck, 1986) and motor slowness, reflected in slower reaction time (RT) and movement time (MT) in patients compared to normal controls (Straube and Oades, 1992; Mannuzza et al., 1984; Elkins and Cromwell, 1994; Nestor et al., 1992, Fuller and Jahanshahi, 1999) have been reported in schizophrenia; patients with schizophrenia do not have major deficits in bimanual co-ordination. In contrast, in a previous study in Parkinson’s disease (Brown and Jahanshahi, 1998) the patients showed greater decline in bimanual performance than normals.

An interesting finding is that under dual task conditions, the performance of the patients with schizophrenia in peg placement actually improved relative to the unimanual pegboard task. The patients with schizophrenia were able to place more pegs while performing a secondary task with their other hand. In contrast, the tapping decreased compared to the unimanual tapping a decrement that was significantly greater for the patients. Thus the improvement in the visually guided pegboard task was at the expense of the tapping task. Similar results have been found in patients with Parkinson’s disease (Brown and Jahanshahi, 1998; Brown et al., 1993).

Previous studies report that patients with schizophrenia show impaired RTs when a simultaneous cognitive task is introduced (Granholm, et al., 1996; Schwartz et al., 1989;
Schwartz et al., 1991) thus suggesting limited attentional processing capacity. Why does performance on the visually guided task improve in patients with schizophrenia under dual task conditions? Brown and Jahanshahi (1998) provided two alternative explanations of a similar improvement obtained in patients with Parkinson’s disease. The first is that for each task there may be an optimal level of attention such that too much attention is detrimental to skilled performance. For example, thinking about individual movements can impair smooth motor planning and execution such as when running down stairs; or a golfer can greatly impair his or her putt by thinking about each single movement in the motor sequence. It is possible that under dual task conditions by removing some of the ‘excess’ attention, finger tapping makes the attentional allocation to peg placement optimal for the patients so that performance on the latter task improves. The second explanation is that in light of the deficits in schizophrenia in internal generation of action with relative normality of stimulus-driven behaviour (Frith, 1992; Fuller et al., 1999) rhythmical tapping acts as an external pacing cue that improves the visually guided pegboard. Thus it is possible that the patients are improving peg placement by using the rhythm of tapping as a pacing stimulus. Brown and Jahanshahi (1998) suggested that the first explanation can be tested by varying the cognitive load of a non-motor secondary task for example, mental arithmetic, while the second explanation can be tested by manipulating the timing characteristics of the secondary tapping task. For patients with schizophrenia some evidence relating to these already exists. Granholm et al. (1996) used a visual search task, involving pointing at a screen when a target appeared as the primary task and a simple RT as the secondary task. Thus the primary task, although visually guided, had a less demanding motor output component than the pegboard task in this study, and the secondary RT task did not involve any rhythmic cueing. The patients with schizophrenia did not improve performance on the primary visual search task in the dual task condition but in fact
showed a greater secondary task decrement (RT slowing) than controls in the highest processing load dual task condition. Therefore, in the present study it is more likely that the patients are using the rhythmic finger tapping as an external pacing cue to improve performance of the visually guided task.

There is evidence that as suggested by Frith (1992) patients with schizophrenia, especially those with high ratings of negative signs, are impaired in self-generated movements but not externally-triggered (Fuller et al., 1999). However, higher ratings of incoherence were associated with reduced peg placement in the dual task condition, suggesting that this symptom may play a role in the decrement in tapping performance seen in the dual task. The fact that covarying out MMS and BDI scores eliminated all significant differences between the patients and normal subjects suggests that the impairments in performance seen in the group with schizophrenia are associated with higher levels of depression and cognitive impairment.

Both Parkinson’s disease and schizophrenia are characterised by symptoms such as akinesia or poverty of action and speech, deficits that reflect impairment of willed actions (Jahanshahi and Frith, 1998). Despite similarities, differences between patients with schizophrenia and Parkinson’s disease are also evident. In a previous study with patients with Parkinson’s disease an improvement for peg placement at the expense of tapping was observed, similar to that in the present study, but the Parkinson’s patients also showed greater impairment in the bimanual tasks than in the unimanual tasks compared to normals (Brown and Jahanshahi, 1998), which was not found for the patients with schizophrenia. The similarity in the dual task condition between the two patient groups with fronto-striatal involvement (Jahanshahi et al., 1995; Weinberger et al., 1986), may reflect the greater dependence of both groups on visual signals and their
reliance on rhythmic tapping as an external cue to improve peg placement. In conclusion the results of the current study revealed qualitatively different pattern of motor performance in schizophrenia under dual task conditions which was associated with higher ratings of negative signs.
CHAPTER 4

Study 3: Movement-Related Potentials prior to self-initiated and externally triggered movements

4.1 Introduction

Movement-related potentials (MRPs) are electrophysiological measures recorded over the scalp, which reflect preparatory processes prior to movement. The Bereitschaftspotential (BP) is a negative MRP occurring 1 to 1.5 seconds prior to a self-paced movement (Kornhuber and Deecke, 1965). The BP is considered to consist of three components, the early BP, with onset 1 – 1.5 seconds prior to the movement onset, the late BP, which occurs about 500 ms prior to movement onset, and the peak BP, which either coincides with or occurs about 50 ms prior to the onset of movement (Deecke et al., 1969, 1976).

Libet et al. (1982, 1983) suggested that two volitional processes contribute to the BP. The first, which in terms of its timing corresponds to the early component, is considered to reflect volitional motor preparatory processes associated with the development of preparation to act in the near future. The second which in terms of its timing corresponds to the late component is associated with voluntary choice and with the endogenous ‘urge’ or intention to act. With self-paced or self-initiated movements the early, late, and peak BP components are present (Kutas and Donchin, 1980; Thickbroom et al., 1985; Papa et al., 1991; Aminoff et al., 1993; Jahanshahi et al., 1995); reflecting the preparation involved in planning to move, as well as the endogenous intention to act (Jahanshahi et al., 1995). Previous studies have shown that with externally-triggered movements, if the stimulus occurs regularly and can be
anticipated, motor preparation is possible and some pre-movement negativity is present (Kutas and Donchin, 1980; Thickbroom et al., 1985; Papa et al., 1991; Aminoff et al., 1993; Jahanshahi et al., 1995). With regularly triggered movements, however, the decision when to move is not self-generated, but is determined by the onset of the triggering stimulus. Therefore, it can be suggested that the late component in a regularly paced externally-triggered movement is lower than in a self-initiated movement because the late component reflects only the maintenance of motor preparation without volitional decision making about when to act (Jahanshahi et al., 1995). With externally-triggered movements, if stimulus presentation is irregular and its onset cannot be anticipated and motor preparation is not as viable then there is no pre-movement negativity, only the final activation of the motor cortex seen in the peak BP (Aminoff et al., 1993; Jahanshahi et al., 1995).

Several studies have investigated the BP in schizophrenia and found impaired BPs compared to normals (Bachneff and Engelsman, 1983; Chiarenza, 1985; Singh et al., 1992; Karaman et al., 1997). However, the results of these studies are contradictory. For example, while some previous studies have found both the early and late BP to be reduced in schizophrenia (Singh et al., 1992) others report the early BP to be reduced in patients with positive symptoms and the late BP to be reduced in patients with negative signs (Karaman et al., 1997). There have also been reports that medicated patients with schizophrenia with tardive dyskinesia have larger BP amplitude compared to controls while patients with schizophrenia without tardive dyskinesia did not differ from normals (Adler et al., 1989). While some studies have shown a longer BP duration in schizophrenia (Westphal et al., 1986), others reported a shorter BP duration in schizophrenia which was found to be associated with flattening of affect (Bachneff & Engelsman, 1983). Recently patients with schizophrenia have shown reduced BPs prior
to movement selection compared to normal controls but the patients did show an increase of BP amplitude relative to task difficulty (Dreher et al., 1999).

On theoretical grounds impairment of BPs would be expected in patients with predominantly negative signs. The aim of study 3 was to compare MRPs prior to self-initiated and externally-triggered movements in three groups: normal controls, patients with schizophrenia ranking high on negative signs, and patients with schizophrenia ranking high on positive symptoms. It was predicted that the main differences would be found between the normals and patients with negative signs prior to self-initiated movements and that fewer or no group differences would be evident for MRPs prior to externally-triggered movements or the group with predominately positive symptoms compared with the normals.

4.2 Method

4.2.1 Design
A mixed between groups and within-subject design was used. Three groups of subjects took part in the experiment: normal controls, patients with schizophrenia with high ratings of positive symptoms and patients with schizophrenia with high ratings of negative signs. There were three experimental conditions (self-initiated, externally-triggered, and rest).

4.2.2 Subjects
Table 4.1 shows the characteristics of the samples. Thirteen patients diagnosed with schizophrenia according to DSM IVR were recruited from the National Hospital for Neurology and Neurosurgery. The data of two patients were excluded, one because of excessive movement and one due to excessive EOG artifact. The data from the remaining eleven patients were used in the analysis. Each patient was rated on the
Krawieka Manchester Scale, a 4-point standardised psychiatric assessment scale (Krawieka et al, 1977) for current positive symptoms and negative signs. Those subjects who had a higher rating of positive symptoms (incoherence, delusions and hallucinations, maximum total score = 12) compared to negative signs (poverty of speech, flattened affect and psychomotor retardation, maximum total score = 12) were placed in the 'positive' group (4 male, 2 female). Those with a higher negative compared to positive score were placed in the 'negative' group (5 male). For both groups, the mean scores for positive symptoms and negative signs differed significantly (p < 0.05). The two groups did not differ significantly in terms of duration of illness (p > 0.05). Two patients in the positive schizophrenia group were not on medication, while all other patients were. The two groups did not differ significantly for mean dose of anticholinergic or neuroleptic medication (p > 0.05).

Seven healthy normals with no previous history of psychiatric or neurological illness, head injury, or drug abuse were tested. One normal subject's data were excluded due to excessive EOG artifact. The data from the other 6 normals (1 male, 5 female) were used for analysis. To screen for cognitive deficits, the Mini Mental State Examination (Folstein et al., 1975) was administered to all subjects. None of the subjects scored below the cut-off of 25, indicative of cognitive deficit. All subjects were right handed except for one (positive schizophrenia group) who was ambidextrous. The three groups were matched on age and handedness (Oldfield, 1971) and did not differ in terms of scores on the Beck Depression Inventory (BDI) (Beck et al, 1961) or the Mini Mental State Examination (MMSE) (p > 0.05). The three groups did differ in terms of proportion of males to females ($X^2 = 8.06$, d. f. = 2, p = 0.02).
Table 4.1. The Details of the three subject groups. Values given are means; standard deviations are in brackets

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Positive Schizophrenia</th>
<th>Negative Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex male : female</strong></td>
<td>1:5</td>
<td>4:2</td>
<td>5:0</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>44 (14.3)</td>
<td>42 (7.9)</td>
<td>38 (4.6)</td>
</tr>
<tr>
<td>Mini Mental State Examination</td>
<td>30.0 (0.0)</td>
<td>28.5 (2.0)</td>
<td>29.2 (1.3)</td>
</tr>
<tr>
<td>(0- 30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory (max</td>
<td>9.3 (3.6)</td>
<td>14.2 (12.6)</td>
<td>11.2 (8.4)</td>
</tr>
<tr>
<td>- 63)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handedness (-100 = purely left,</td>
<td>75 (18.0)</td>
<td>77 (14.0)</td>
<td>90 (8.9)</td>
</tr>
<tr>
<td>100 =purely right handed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (years)</td>
<td>17.2 (8.2)</td>
<td>12.0 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Positive symptoms (hallucination,</td>
<td>6.7 (4.0)</td>
<td>1.0 (1.7)</td>
<td></td>
</tr>
<tr>
<td>delusions, incoherence) (0 - 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative signs (poverty of</td>
<td>2.8 (3.8)</td>
<td>4.4 (4.4)</td>
<td></td>
</tr>
<tr>
<td>speech, flattened affect,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>psychomotor retardation) (0 – 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose anticholinergic, Disipal</td>
<td>50.0 (54.8)</td>
<td>80.0 (130.4)</td>
<td></td>
</tr>
<tr>
<td>equivalent [range]</td>
<td>[0 – 100 mg]</td>
<td>[0 – 300 mg]</td>
<td></td>
</tr>
<tr>
<td>Dose neuroleptic, chlorpromazine</td>
<td>128.3 (123.3)</td>
<td>316.0 (295.9)</td>
<td></td>
</tr>
<tr>
<td>equivalent [range]</td>
<td>[0 – 320 mg]</td>
<td>[100- 800 mg]</td>
<td></td>
</tr>
</tbody>
</table>
4.2.3 Procedure
Informed consent was obtained from all subjects. MRPs were recorded in three experimental conditions.

4.2.3.1 Self-initiated movements
Subjects made self-initiated movements at an average rate of once every three seconds. The movement involved a brisk lifting of the right index finger. The subject's finger rested on a zero force touch switch. Extension of the finger interrupted contact with the switch. Inter-response intervals were measured to the nearest millisecond. A tone, which subjects were told to ignore, was presented 100 ms after the self-initiated movement. This was to control for the tone effect in the externally-triggered condition.

4.2.3.2 Externally-triggered movements
Subjects made the same finger lifting movement in response to a tone presented at an identical rate to that generated by the subjects in the self-initiated condition: i.e. the rate of movement was yoked to that generated by the subject in the self-initiated condition. This was achieved by saving the inter-response intervals produced by the subject in the self-initiated condition on the computer, which were then used as the inter-stimulus-intervals for presentation of the tone in the externally-triggered and rest conditions. Reaction times (time from presentation of tone to subject lifting finger) were measured to the nearest millisecond.

4.2.3.3. Rest
Subjects listened to tones presented at a rate yoked to condition (i). No response was required. This condition was included to control for the sensory potentials evoked by the tone in condition (ii).
Because of the necessity of yoking the rate of tone presentation to the rate of self-initiated movements, a fixed order was used. In each block, subjects performed the self-initiated condition, then the externally-triggered condition, followed by the rest condition. Four blocks of 60 trials of each condition were performed.

4.2.4 Recording of MRPs

The subject sat in a comfortable reclining chair in a quiet, dimly lit room. All recordings were made with Digitimer D150 amplifiers. The EEG was recorded using non-polarizable Ag/AgCl electrodes. The electrode positions were a modification of the International 10-20 convention, with placements at F3, Fz, F4, FC3, FCz (4 cm anterior of vertex), FC4, C3, Cz (vertex), C4, P3, Pz, P4. Electrodes were secured to the scalp with collodion. Linked earlobes served as the reference. The subject was grounded on the left wrist. The high frequency cut-off was set at 100 Hz., the low frequency cut-off was 0.03 Hz., with a time constant of 5 seconds. The electro-oculogram (EOG) was recorded from electrodes placed at the glabella and on the outer canthus of the right eye. For recording of EOG the high frequency cut-off was 100 Hz., a low frequency cut-off of 0.16 Hz, with a time constant of 1 second. Trials with EOG above 20 μV were excluded on line and the data collection continued until 60 artifact free trials were recorded. The EMG was recorded using a bipolar arrangement from the prime mover that was the extensor indicis proprius. For EMG recording a high frequency cut-off of 3 kHz, a low frequency cut-off of 53 Hz., and a time constant of 0.03 seconds was used. The EMG was rectified and integrated and was used for back-averaging of the EEG on a trial by trial basis.

The duration of the sampling window was 2500, 2000 ms before and 500 ms after the EMG onset. The sampling rate was 150 Hz (a total of 375 data points, 300 data points prior to EMG onset). For the rest condition, where there was no response, the tone
acted as the trigger for sampling the EEG data. The analogue data were digitized to 12-bit resolution using a CED-1401 general purpose laboratory interface (Cambridge Electronic Design, Cambridge, UK, 1988). Data collection was controlled using the SigAvg programmes (version 6.03; Cambridge Electronic Design, 1993). Prior to off-line analysis of the MRP data, any remaining trials with EOG or movement artifact were eliminated and the records were back-averaged using the EMG onset on a trial by trial basis. The minimum number of valid trials was 100.

4.2.5 Analysis of MRPs
In the externally-triggered condition, all measurements were obtained from the subtracted waveforms: i.e. traces from which the sensory components ($N_{100}$, $P_{200}$, $N_{200}$) elicited to the tone alone in the rest condition had been subtracted to obtain a 'pure' measure of movement-related negativity. This subtraction process involved a number of steps. First, for each subject, the sensory components to the tone in the rest condition were reworked by offsetting them with the reaction time of the subject on a trial-by-trial basis. Thus, the potentials evoked by the tone were spread by the variability of the subject's reaction time. Then the onset of the tone in the triggered condition was superimposed on the onset of the tone in the reworked rest condition, which aligned the sensory components in the two conditions. Finally the EEG data were subtracted, leaving the pre-movement potentials in the two externally-triggered conditions without the sensory components due to tone. The movement-related components preceding the movement onset, which were of primary interest, were not altered by the subtraction process, which simply subtracted the negativity associated with the presentation of the tone trigger. This procedure was not carried out using the self-initiated data since the tone was present after EMG onset and thus not interfering with the movement-related components of interest.
For scoring the BP prior to the self-initiated movements, procedures similar to those previously employed in our laboratory (Dick et al., 1987, 1989; Jahanshahi et al, 1995) were used. Only the three pre-movement components of the MRPs, i.e., the early, late and peak BPs were measured. To determine the onset of each of the three components, printouts of the averaged waveform for each subject and each type of movement were examined independently by three scientists who had experience with BPs. For each record, the point of onset of the early, late and peak BP components were marked using Cz as the main reference trace. The onset of each component for each subject and each type of movement was determined by taking the consensus point. Using the marked points, the mean latency of the early BP (rise of the slope from baseline), the late (point of change in slope) and the peak BP (most negative point at or prior to EMG onset) onset were measured in relation to EMG. The amplitudes of the early and peak BP were measured, and using these values the amplitude of the late BP was calculated through subtraction. Amplitudes were measured in relation to a 300-ms baseline which was obtained by averaging the traces between the point of onset of the early BP and the preceding 300 ms.

The onset of the early and late components were not clear in every trace for the externally-triggered waveforms. Therefore, the points of onset of the early and late components from the self-initiated data were used to mark the onset of these components in the externally-triggered waveforms for all subjects. The peak BPs, however were clearly visible in the externally-triggered data, so these points were marked for each subject’s trace.

The slope of the early component was measured between the point of onset of the early BP and the onset of the late BP. The slope of the late component was measured from
the point of onset of the late BP to the onset of the peak BP. The slopes were measured in \( \mu V \) per second.

The data for each component of the MRP (early, late and peak) were analysed separately for the self-initiated and the externally-triggered responses using repeated measures analysis of variance (ANOVA). In each ANOVA, Group (normals, patients with positive symptoms, patients with negative signs) was the between subjects variable and Electrode Site (F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, P3, Pz, P4) was the within-subjects repeated measures variable. The slope of the early BP and the slope of the late BP were also analysed using similar repeated measures ANOVA. Where necessary, to deal with violations of assumptions of sphericity, the Greenhouse-Geisser epsilon was used to adjust the degrees of freedom. Pre-planned special contrasts were carried out comparing the normals with the patients with negative signs and the normals with the patients with positive symptoms. In order to examine the data further independent t-tests were used for post hoc examination of the two patient groups. All statistics were carried out using SPSS for Windows version 8.0.

4.3 Results

4.3.1 Behavioural data

Mean inter-response intervals for the self-initiated condition and reaction times for the externally-triggered are presented in Table 4.2. The three groups did not differ significantly for the inter-response intervals \([F(2,14) = 1.58, p = 0.24]\) or reaction times \([F(2, 14) = 1.01, p = 0.37]\). The important aspect of the behavioural data is that all three groups produced self-initiated movements at the target rate of on average once every 3 seconds. Since the rate of movement for the externally-triggered condition was yoked to the self-initiated condition, this means that the three groups did not differ in terms of the rate of movement in the triggered condition either.
Table 4.2. The mean behavioural data for the three groups for the self-initiated and the externally triggered movements. Values given are means; standard deviations are in brackets. The units are milliseconds. IRI = inter-response interval; RT = reaction time.

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Positive Schizophrenia</th>
<th>Negative Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self Initiated IRI</td>
<td>3274.8 (261.8)</td>
<td>3080.7 (300.8)</td>
<td>3032.6 (94.3)</td>
</tr>
<tr>
<td>Externally-Triggered RT</td>
<td>204.2 (75.0)</td>
<td>166.3 (48.6)</td>
<td>237.0 (111.7)</td>
</tr>
</tbody>
</table>

4.3.2 Latencies

Table 4.3 contains the latencies for each group. For the self-initiated movements, there were no significant differences among the three groups for latencies of the early [F(2,14)= 1.88, p = 0.19], late [F(2,14) = 0.55, p = 0.59], or peak [F(2,14) = 0.01, p = 0.99] BP. For the externally-triggered movement the latency of the peak BP did not differ significantly among the three groups [F(2,13)= 1.51, p= 0.26].

Table 4.3. The mean latencies for the groups for the self-initiated and externally-triggered movements. Values given are in milliseconds and are measured relative to EMG onset; standard deviations are in brackets. BP = Bereitschaftspotential.

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Positive Schizophrenia</th>
<th>Negative Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self Paced Early BP</td>
<td>-1187.5 (82.3)</td>
<td>-1024.5 (233.5)</td>
<td>-1191.4 (146.3)</td>
</tr>
<tr>
<td>Late BP</td>
<td>-448.8 (75.4)</td>
<td>-400.0 (80.0)</td>
<td>-482.4 (213.1)</td>
</tr>
<tr>
<td>Peak BP</td>
<td>-44.5 (29.7)</td>
<td>-45.4 (26.5)</td>
<td>-46.6 (17.0)</td>
</tr>
<tr>
<td>Externally-Triggered Peak BP</td>
<td>-41.0 (31.4)</td>
<td>-43.2 (22.7)</td>
<td>-70.2 (30.4)</td>
</tr>
</tbody>
</table>
4.3.3. Amplitudes
The waveforms of the MRPs prior to the self-initiated and externally-triggered movements are shown in Figures 4.1 and 4.2. The waveforms of the MRPs preceding self-initiated movements for one patient from the 'positive' group with the highest levels of medication and the one patient from the 'negative' group with lower levels of medication are presented in Figure 4.3.

4.3.3.1 MRPs prior to self-initiated movements
For the early component the main effects of Group and Electrode Site and the Group x Electrode Site interaction were not significant (p > 0.05). For the late component the main effects of Group [F(2, 14) = 3.90, p = 0.05] and Electrode Site [F(3, 43) = 7.44, p = 0.001] reached significance but the Group x Electrode Site interaction did not (p > 0.05). For the peak component the main effects of Group [F(2, 14) = 5.20, p = 0.02] and Electrode Site [F(3, 42) = 7.95, p = 0.001] reached significance but the Group x Electrode Site interaction did not (p > 0.05).

Pre-planned special contrasts revealed that the mean amplitudes of the MRPs prior to self-initiated movements for the late and the peak components were significantly lower in the patients with negative signs than in the normal controls (p < 0.05), but there was no significant difference between the normal controls and the patients with positive signs (p > 0.05). Post hoc t-tests revealed that the amplitude of the early and late components did not differ significantly between the two patient groups (p > 0.05). Further investigation of the main effect of Electrode Site revealed that for the amplitude of the late component, the amplitude was most negative at FCz, Cz and C3. For the peak component the amplitude reached greatest negativity at FCz, Cz and FC3.
4.3.3.2 MRPs prior to externally-triggered movements

For the early, late and peak components there were no significant main effects of Group (p > 0.05) and no significant Group x Electrode Site interactions (p > 0.05). There was a significant main effect of Electrode Site for the amplitude of the late [F(4, 49) = 2.91, p = 0.04] and peak components [F(4,50) = 3.53, p = 0.01]. Further post-hoc examination of the Electrode Site effect revealed that for the late component the highest negativity was at Fz, FCz and FC3 while for the peak component the highest negativity was present at FCz, Fz and FC3.

4.3.4 Slopes

4.3.4.1 MRPs prior to self-initiated movements

For the self-initiated movements, for the slope of the early component, the main effect of Group [F(2, 14) = 5.14, p = 0.02] was significant, but the main effect of Electrode Site and the Group x Electrode Site interaction did not reach significance (p > 0.05).

For the slope of the late component prior to the self-initiated movements, the main effects of Group [F(2, 14) = 4.52, p = 0.03] and Electrode Site were significant [F(5, 59) = 6.96, p = 0.01], but the Group x Electrode Site interaction was not (p > 0.05).

Pre-planned special contrasts revealed that prior to self-initiated movements the slope of the early and late components were significantly reduced in the patients with negative signs compared to normals (p < 0.02) and did not differ significantly between the patients with positive symptoms and the normals (p > 0.50). Post hoc t-tests revealed that the slope of the early component was significantly reduced in the patients with negative signs compared to the patients with positive symptoms (t = 3.2, d.f. = 8, p = 0.01) but the slope of the late component did not differ significantly between the two patient groups (p = 0.1).
Figure 4.1. Grand averages of the movement-related potentials preceding self-initiated movements for the normals (dark lines), patients with positive schizophrenia (light lines) and negative schizophrenia (dotted lines).
Figure 4.2. Grand averages of the movement-related potentials preceding externally-triggered movements for the normals (dark lines), patients with positive schizophrenia (light lines) and negative schizophrenia (dotted lines).
Figure 4.3. Averaged movement-related potentials preceding self-initiated movements for one patient from the 'positive' group (black thin dotted line) with high levels of medication (anticholinergic dose = 100 mg, neuroleptic dose = 320 mg) and one patient from the 'negative' group (thick solid line) with low levels of medication (anticholinergic dose = 0 mg, neuroleptic dose = 130 mg).
Further examination of the main effect of Electrode Site for slope of the late component revealed that the Electrode Sites of greatest negativity were FCz, FC3, and Cz.

### 4.3.4.2 MRPs prior to externally-triggered movements

For the externally-triggered movements, there were no significant main effects of Group or Electrode Site or their interaction for either the early or the late slope ($p > 0.10$).

### 4.3.5 Correlational analysis

The amplitude of the early, late, and peak components and the slope of the early and late components of the MRP prior to self-initiated movements were correlated with medication using Pearson’s correlation coefficients. For the patients with schizophrenia, no relationship was found between duration of illness and MRP amplitudes or slopes ($p > 0.05$). There was a significant *positive* correlation between dose of anticholinergic medication and the amplitude of the late component at Pz ($r = 0.64$, $p = .04$) and a significant *negative* correlation between dose of anticholinergic medication and the slope of the early component at Pz ($r = -0.62$, $p = 0.03$) for the MRP prior to self-initiated movements. This means that higher doses of anticholinergic medication were associated with lower amplitude of the late BP, yet larger slope of the early BP at Pz. There was a significant *negative* correlation between dose of neuroleptic medication and the slope of the early component of the MRP prior to self-initiated movements at the three fronto-central sites (FC3, FCz, FC4) and at Pz (range of $r$ -0.64 to -0.78, $p <0.04$). This means that higher doses of neuroleptic medication were associated with lower slopes of the early BP.

The amplitude of the early, late, and peak components and the slope of the early and late components of the MRP prior to self-initiated and externally-triggered movements were correlated with the individual symptom ratings of the Krawieka Manchester Scale and
depression as rated on the Becks Depression Interval (BDI) using Pearson’s correlation coefficients. The significant correlations are presented in Table 4.4. After the Bonferroni correction for the number of correlations (600) there were no significant correlations.

There is a possibility that factors such as depression, medication or cognitive deficits could confound the findings of correlational analyses. Therefore, Pearson’s Partial Correlations were run controlling for dose of neuroleptic, BDI score, and Mini Mental score and the significant correlations are presented in Table 4.5. After the Bonferroni adjustment for number of correlations (480) there were no significant correlations.
Table 4.4. Pearson’s correlations between individual symptom ratings and the amplitude and slope of the MRP components prior to Self initiated (SI) and Externally Triggered (ET) movements. (BP = Bereitschaftspotential)

<table>
<thead>
<tr>
<th>Symptom Rating</th>
<th>BP measure</th>
<th>Site</th>
<th>r value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI Poverty of speech</td>
<td>Amplitude of the early BP</td>
<td>FCz, FC4, C3, C4, Cz, C4, Pz</td>
<td>Range -0.59 to -0.72</td>
<td>0.04</td>
</tr>
<tr>
<td>Depression</td>
<td>Amplitude of the early BP</td>
<td>P4</td>
<td>-0.56</td>
<td>0.05</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Amplitude of the late BP</td>
<td>FCz</td>
<td>0.62</td>
<td>0.03</td>
</tr>
<tr>
<td>Incoherence</td>
<td>Amplitude of the peak BP</td>
<td>Fz</td>
<td>0.56</td>
<td>0.05</td>
</tr>
<tr>
<td>Incoherence</td>
<td>Slope of the early BP</td>
<td>Fz, FC3</td>
<td>0.76, 0.73</td>
<td>0.01</td>
</tr>
<tr>
<td>Delusions</td>
<td>Slope of the early BP</td>
<td>Fz</td>
<td>0.68</td>
<td>0.01</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Slope of the early BP</td>
<td>FC3</td>
<td>0.58</td>
<td>0.04</td>
</tr>
<tr>
<td>ET Poverty of speech</td>
<td>Amplitude of the late BP</td>
<td>C4</td>
<td>0.62</td>
<td>0.03</td>
</tr>
<tr>
<td>Depression</td>
<td>Amplitude of peak BP</td>
<td>C4, P3</td>
<td>0.65, 0.62</td>
<td>0.03</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Amplitude of the peak BP</td>
<td>FC4, Cz, C4</td>
<td>Range 0.61 to 0.78</td>
<td>0.04</td>
</tr>
<tr>
<td>Incoherence</td>
<td>Amplitude of the peak BP</td>
<td>Cz, C4, Pz, P4</td>
<td>Range 0.59 to 0.78</td>
<td>0.05</td>
</tr>
<tr>
<td>Poverty of speech</td>
<td>Slope of the early BP</td>
<td>F3</td>
<td>-0.65</td>
<td>0.02</td>
</tr>
<tr>
<td>Flattened affect</td>
<td>Slope of the early BP</td>
<td>F3</td>
<td>-0.59</td>
<td>0.05</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Slope of the early BP</td>
<td>F3</td>
<td>-0.72</td>
<td>0.01</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Slope of the late BP</td>
<td>C3, Cz, C4, P3, Pz, P4</td>
<td>Range 0.60 to 0.66</td>
<td>0.04</td>
</tr>
<tr>
<td>Poverty of speech</td>
<td>Slope of the late BP</td>
<td>FCz, FC4, Cz, C4, Pz</td>
<td>Range 0.58 to 0.73</td>
<td>0.05</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Slope of the late BP</td>
<td>FCz, C3, Cz, C4, Pz</td>
<td>Range 0.58 to 0.71</td>
<td>0.02</td>
</tr>
<tr>
<td>Flattened affect</td>
<td>Slope of the late BP</td>
<td>C4</td>
<td>0.68</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Table 4.5 Significant \((p < 0.05)\) results of the Pearson’s Partial correlational analysis between the amplitudes and slopes of the early, late and peak BP in the Self initiated (SI) and Externally Triggered (ET) conditions controlling for medication, level of depression, and Mini Mental score. \((BP = \text{Bereitschaftspotential})\)

<table>
<thead>
<tr>
<th>Symptom Rating</th>
<th>BP measure</th>
<th>Site</th>
<th>r value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poverty of speech</td>
<td>Amplitude of the early BP</td>
<td>C3, C4</td>
<td>-0.76 to -0.70</td>
<td>0.04</td>
</tr>
<tr>
<td>Depression</td>
<td>Amplitude of the late BP</td>
<td>P4, Pz</td>
<td>-0.78, -0.66</td>
<td>0.05</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Amplitude of the late BP</td>
<td>P4</td>
<td>-0.71</td>
<td>0.03</td>
</tr>
<tr>
<td>Flattened affect</td>
<td>Amplitude of the peak BP</td>
<td>C3, C4, P3, Pz</td>
<td>Range -0.67 to</td>
<td>0.05</td>
</tr>
<tr>
<td>Delusions</td>
<td>Slope of the early BP</td>
<td>Fz</td>
<td>0.74</td>
<td>0.02</td>
</tr>
<tr>
<td>Depression</td>
<td>Slope of the early BP</td>
<td>Cz</td>
<td>0.74</td>
<td>0.02</td>
</tr>
<tr>
<td>Incoherence</td>
<td>Slope of the early BP</td>
<td>P4</td>
<td>0.77</td>
<td>0.02</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Slope of the peak BP</td>
<td>F4</td>
<td>-0.72</td>
<td>0.03</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Slope of the early BP</td>
<td>F3</td>
<td>-0.71</td>
<td>0.05</td>
</tr>
<tr>
<td>Flattened affect</td>
<td>Amplitude of the peak BP</td>
<td>C3, C4, P3, Pz</td>
<td>Range -0.67 to</td>
<td>0.05</td>
</tr>
<tr>
<td>Delusions</td>
<td>Slope of the early BP</td>
<td>F3, P3</td>
<td>-0.75, -0.79</td>
<td>0.03</td>
</tr>
<tr>
<td>Poverty of speech</td>
<td>Slope of the early BP</td>
<td>F3, C3, C4, Pz</td>
<td>Range 0.71 to</td>
<td>0.05</td>
</tr>
<tr>
<td>Delusions</td>
<td>Slope of the late BP</td>
<td>P3</td>
<td>0.80</td>
<td>0.02</td>
</tr>
<tr>
<td>Flattened affect</td>
<td>Slope of the late BP</td>
<td>C4</td>
<td>0.71</td>
<td>0.05</td>
</tr>
</tbody>
</table>

4.4 Discussion

The present results showed that prior to self-initiated movement relative to normals, the amplitude of the late and peak BP and the slope of the early and late BP were significantly lower for patients with predominance of negative signs but not patients with predominance of positive symptoms. Also, prior to self-initiated movement the
slope of the early component was significantly lower for the patients with negative signs than patients with predominance of positive symptoms. The three groups did not differ significantly in MRPs recorded prior to externally-triggered movements. No significant differences were discovered between the normals and patients in the behavioural results (inter-response interval or reaction times). Although the EMGs among the groups appear different this is unlikely to affect MRPs as it has been shown that BPs are not affected by changes in the amplitude or velocity of finger movements (Dick et al., 1987). Thus, the differences seen in the MRPs cannot be attributed to differences in performance by the patients.

The current results concur with previous studies showing abnormal MRPs in schizophrenia (Timsit-Berthier et al., 1973; Chiarenza et al., 1985, Westphal et al., 1986, Singh et al., 1992; Karaman et al., 1997; Dreher et al., 1999). However, the present results also extend previous findings in two important respects. First, the current results showed that the deficits in MRPs prior to self-initiated movements are particularly evident for patients with predominance of negative signs whereas the patients with predominance of positive symptoms did not differ significantly from normals. The amplitudes at some sites (e.g. FCz) do appear lower in the patients with positive symptoms compared to controls, but these differences were not large enough to reach statistical significance. Future studies with greater numbers of participants may clarify these differences. Second, the current results demonstrated that differences from normal MRPs were present for patients with negative signs only prior to self-initiated movements requiring self-generated decision making about the precise timing of movements as well as motor preparation but the patients did not differ from normals in terms of MRPs prior to externally-triggered movements.
In contrast to the amplitudes which are based on measurements at a single point in time, the slope of MRPs show changes in negativity over time and for this reason are perhaps more sensitive. In fact, the groups of patients with predominance of positive symptoms or negative signs only differed significantly in terms of the early slope, which is considered to reflect motor preparatory processes associated with SMA activation (Deecke et al, 1969; 1976). This suggests that motor preparatory processes are more impaired in patients with schizophrenia and negative signs. As the two patient groups did not differ significantly in terms of the late slope, which according to Libet's (1982) distinction coincides with the time course of volitional decision-making and intention to act, one inference would be that these processes are impaired in patients with schizophrenia regardless of the type of symptomatology.

Motivation is one of the variables shown to affect the BP (McAdam & Seales, 1969). Although the deficits in MRPs in disorders such as Parkinson's disease and schizophrenia are traditionally related to the motor symptoms of the former disorder such as akinesia and bradykinesia and the less conspicuous motor abnormalities in schizophrenia such as clumsiness, disorganisation and slowness of movements (Manschreck, 1986); nevertheless it is also possible that motivational deficits such as apathy which can be a feature in both disorders and may also reflect fronto-striatal dysfunction (Jahanshahi & Frith, 1998) can also contribute to the deficits of MRPs observed in these disorders.

Studies in Parkinson's disease (Dick et al, 1989; Jahanshahi et al, 1995) have shown that it is the amplitude of the early BP which is lower than normal in patients with Parkinson's disease. In contrast, for patients with schizophrenia and negative signs both the early and late components are impaired relative to normals (Singh et al, 1992;
present study). These results suggest that the different MRP components are
differentially sensitive to different disorders such as Parkinson's disease and
schizophrenia in which impairment of fronto-striatal circuits are implicated. The
differential sensitivity of the MRP components is also supported by the fact that
dopaminergic medication increases and anti-dopaminergic medication decreases the
amplitude of the *early* BP only (Dick et al, 1987). In the present study we found that
dose of neuroleptic medication had a significant negative correlation with the slope of
the early MRP component prior to self-initiated movements which suggests that those
patients on higher levels of neuroleptic medication had reduced slopes for the early BP.
The patients with predominance of negative signs were taking higher doses of
neuroleptic medication than those with high positive symptoms, although the difference
in dosage was not statistically significant. Nevertheless, given that anti-dopaminergic
medication has been shown to reduce the amplitude of the early BP (Dick et al, 1987), it
is possible that the significant reduction of the early slope in patients with high negative
ratings relative to normals, partly relates to their higher doses of neuroleptic medication.
However, medication can not be the only reason for reduction of MRPs in these patients
as our sample of patients with positive symptoms who were also on neuroleptics did not
significantly differ significantly from normals in terms of MRPs. Also previous studies
have reported reduced amplitude of the early and peak BP in both medicated and
unmedicated patients with schizophrenia (Karaman et al, 1997). Animal studies have
shown that cortical potentials are cholinergic dependent (Pirch et al, 1986). The two
patient groups did not differ significantly in terms of dose of anticholinergic medication,
but the patients with higher ratings of negative signs had higher levels of anticholinergic
medication, which could possibly contribute to the reduced amplitudes of MRPs
observed. But, as shown in Figure 4.3, a patient with high 'positive' symptoms who
was on the highest doses of anticholinergic and neuroleptic medication had larger
amplitudes of MRPs prior to self initiated movements relative to a patient with high 'negative' signs who was on a lower dose of medication. Nevertheless, the possible contributions of neuroleptic and anticholinergic medication to MRPs in schizophrenia need to be more systematically assessed in future studies.

This study showed that patients with higher ratings of negative signs had reduced MRPs prior to self-initiated movements but not externally-triggered movements while the MRPs of the patients with higher ratings of positive symptoms were not impaired significantly for either type of movement. These findings support Frith’s (1992) hypothesis that patients with schizophrenia, particularly those with negative signs, are impaired in willed actions such as the self-initiated movement of the present study but are not impaired in stimulus driven behaviour such as externally-triggered movements assessed by us. Thus, the current results confirm that the distinction between positive symptoms and negative signs has heuristic value when investigating patients with schizophrenia.
CHAPTER 5

Studies 4 and 5: Behavioural suppression in a go no-go reaction time task in schizophrenia: The effect of choice complexity and target/non-target stimuli similarity on response inhibition

5.1 Introduction

Studies 1 to 3 have provided some evidence that patients with schizophrenia have impairments in willed action. According to Jahanshahi and Frith (1998), besides having difficulty generating actions, impairments in willed action would also be manifested as an inability to suppress habitual or inappropriate responses. Evidence of this failure of willed suppression in schizophrenia has been provided in neuropsychological tests; for example, impaired performance on the Stroop task (Liddle and Morris, 1991) and increased perseverations on the Wisconsin Card Sorting Task (Weinberger et al., 1986).

One of the many tests of attention on which patients with schizophrenia show impaired performance is the ‘Continuous Performance Test’ (Rosvold et al., 1956). There are two versions of this test, in one the target is a single letter or stimulus e.g. X that appears on every trial. In the second version the target is a sequence of two stimuli presented in a particular order for e.g. X only when preceded by and A. The subject must be prepared to respond but withhold the response until the correct imperative stimulus appears. This is considered a test of sustained attention, because the target stimulus appears only a small proportion of the time. Patients with schizophrenia perform poorly on this test (Braff, 1993; Nuechterlein, 1991), and have a lower target detection rate than normals (Nuechterlein et al., 1994). In the CPT identical pairs paradigm (CPT-IP) the subject is required to respond only when two identical shapes or letters appear on successive trials, thus requiring greater target discrimination and
making greater demands on working memory. Patients with schizophrenia are impaired on this version of the CPT task (Cornblatt and Keilp, 1994).

Go no-go RT tasks have similar processing requirements as the CPT paradigm – only responding to particular stimuli and withholding response to other stimuli. Thus in addition to sustained attention, the task involves willed initiation and willed suppression of action. Patients with schizophrenia are reported to be impaired on tasks requiring response suppression, such as the antisaccade task (Fukushima et al., 1994), in which subjects are required to withhold eye movements toward a target and instead move their eyes in the opposite direction.

From this inability to suppress stimulus driven responses, it would be predicted that patients with schizophrenia may also be impaired on go no-go tasks. Impaired performance on go no-go RT tasks has been reported following damage to the dorsolateral prefrontal cortex (Drewe, 1975), the medial frontal cortex (Leimkuhler and Mesulam, 1985) and the head of the caudate nucleus (Godefroy et al., 1996) as well as in patients with Parkinson’s disease whose RTs were differentially slowed as complexity of response choice increased (Cooper et al., 1994).

Studies of rCBF suggest that the ventrolateral prefrontal cortex and the anterior cingulate are key areas involved in suppressing a planned motor response (Krams et al., 1998). There have been several functional imaging studies of go no-go RT paradigms in normals. With MRI it is possible to directly compare activation on go trial with the activation on no-go trials (Humberstone et al., 1997; Konishi et al., 1998). Humberstone et al. (1997) found that the SMA proper was activated only on the go trials signifying motor execution, while the pre-SMA was activated in both the go and the no-go trials,
representing the go no-go decision making processes. In their studies, (Kawashima et al., 1996) and Konishi et al. (1998) and found activation of the right superior or inferior frontal sulcus to be specifically associated with response suppression. However, the results of Konishi et al. (1998) should be accepted with caution because the authors’ subtraction method for analysing the data is potentially flawed. Subtracting the data of a block of ‘all-go trials’ from the data of a block of ‘no-go trials’ does not isolate the purely ‘suppression-related’ areas of activation. A block of ‘all go’ stimuli in an SRT task will involve, for example, advance movement preparation that is not possible in a go no-go task (Fuller and Jahanshahi, 1999; Jahanshahi and Frith, 1998).

The purpose of this study is to examine willed initiation and suppression of movement in patients with schizophrenia by using two go no-go RT tasks. One task examines the effect of increasing complexity of response selection while the second task examines the effect of increasing target/non-target stimuli similarity on go reaction times.

There is considerable evidence that RTs become slower as the process of response selection becomes more complex (Sternberg, 1969). One way in which the complexity of response selection can be altered is by increasing the number of salient stimulus features that define a go stimulus among an array of stimuli presented across trials (Cooper et al, 1994).

Since the time of Woodworth (1938) it has been shown that RTs are slower when stimuli are difficult to distinguish from each other as when non-target ‘distractor’ stimuli are similar to the target and share more features with it. In a CRT task requiring detection of a target among distractors, if the target has a unique single feature, then the RT is short even if the target and distractors have other features in common and
increasing the number of distractors does not influence RT (Egeth et al, 1972). This suggests that items are processed in parallel. In contrast, when the target shares at least one feature with the distractors, then subjects have to look for conjunction of the two features to discriminate the target from non-targets. This prolongs RT which increases linearly with the number of distractors (Treisman & Gelade, 1980).

It is predicted that patients with schizophrenia would perform poorly on the go no-go RT task. Besides slower RTs on go trials (impaired movement initiation), more errors on no-go trials (failure of movement suppression) would be predicted for the patients with schizophrenia than the controls. It is also expected that both increased complexity of the response selection and the increased similarity between the target, ‘go’, and the non-target, ‘no-go’, stimuli will have a differentially greater effect on the RTs of patients with schizophrenia compared to that of the controls.

5.2 Method

5.2.1 Subjects
The characteristics of the samples are presented in Table 5.1. Fourteen subjects clinically diagnosed with schizophrenia according to the DSM III R were tested. Each was seen as an out-patient at the National Hospital for Neurology and Neurosurgery. Each patient was rated on the Scale for Assessment of Positive Symptoms (Andreasen, 1984) and the Scale for Assessment of Negative Symptoms (Andreasen, 1983), standardised psychiatric assessment scales for current positive symptoms and negative signs. Overall, the patients were chronically ill and their symptoms were not very severe. In order to determine the effect of current symptoms on initiation and suppression of movement the patients with schizophrenia were divided into two groups. The median rating for positive symptoms was 9, and patients with ratings of positive symptoms greater than the median rating were placed in one group and those patients
Table 5.1 Details of Subject Groups. Values given are means with standard deviations in brackets.

<table>
<thead>
<tr>
<th></th>
<th>Positive Patients</th>
<th>Negative Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Handedness (-100 = completely left handed, 100 = completely right handed)</td>
<td>46.2 (81.7)</td>
<td>88.9 (19.2)</td>
<td>91.4 (11.6)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>38.1 (10.5)</td>
<td>49.7 (11.9)</td>
<td>39.7 (16.6)</td>
</tr>
<tr>
<td>Estimated Verbal IQ (NART)</td>
<td>106.4 (89.0)</td>
<td>111.6 (15.2)</td>
<td>109.6 (6.7)</td>
</tr>
<tr>
<td>Beck Depression Inventory (0 - 63)</td>
<td>15.4 (11.7)</td>
<td>8.0 (5.4)</td>
<td>5.5 (4.9)</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>18.0 (10.6)</td>
<td>21.3 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Positive symptoms (range 0 - 175)</td>
<td>26.3 (12.3)</td>
<td>2.7 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Negative symptoms (range 0 - 120)</td>
<td>26.0 (14.9)</td>
<td>16.3 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Dose anticholinergic in mg (Disipal equivalent)</td>
<td>64.3 (118.0)</td>
<td>35.7 (74.8)</td>
<td></td>
</tr>
<tr>
<td>Dose neuroleptic in mg (Chlorpromazine equivalent)</td>
<td>235.7 (239.3)</td>
<td>126.8 (116.5)</td>
<td></td>
</tr>
</tbody>
</table>

with ratings of positive symptoms below 9 were placed in the other group. The division of patients and their SAPS and SANS scores are presented in Table 5.2. The two groups differed significantly on ratings of positive symptoms ($t = 4.85$, df = 12, $p < 0.001$) but not negative signs ($p > 0.05$). The first group’s rating of positive symptoms (26.29) did not differ significantly from its rating of negative signs (26.00) ($p > 0.05$). As both the positive and negative symptom ratings were high, this group will be referred to as the ‘high symptom’ group. The second group had significantly higher ratings of negative signs (16.29) than positive symptoms (2.71) ($t = 2.98$, df = 6, $p = 0.03$) and as this group had lower ratings of positive and negative symptoms, will be labelled the ‘low symptom’ group. Thus, although the ‘low symptom’ group had lower ratings of negative signs than the ‘high symptom’ group, the ‘low symptom’ group
includes patients whose primary symptoms are negative signs, whereas the 'high symptom' group includes patients suffering from both positive symptoms and negative signs.

Table 5.2 Ratings from the Scale for the Assessment of Positive Symptoms (Andreasen, 1984) and the Assessment of Negative Symptoms (Andreasen, 1983) for the patients, subdivided into two groups.

<table>
<thead>
<tr>
<th></th>
<th>Positive symptoms</th>
<th>Negative signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Symptom Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>P2</td>
<td>47</td>
<td>5</td>
</tr>
<tr>
<td>P3</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>P4</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>P5</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>P6</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>P7</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td><strong>Low Symptom Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>N2</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>N3</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>N4</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>N5</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>N6</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>N7</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

Fourteen healthy normals with no previous history of psychiatric or neurological illness, head injury, or drug abuse were tested. Two normal controls had movement times (MTs) which were extreme compared to group means, one control subject on 40% and one control subject on 50% of the measures of interest. These two cases were therefore excluded. The Mini Mental State Examination (Foltstein et al., 1975) was administered to all subjects and none of the subjects scored below the cut-off of 25 indicative of cognitive deficit.
5.2.2 Procedure

Responses were made on a response box with two buttons. A red button acted as the 'home' key. Four inches above the red button was a green 'response' button. Stimuli were presented on a 14 inch computer screen. Reaction time (RT) was measured (in ms) as the time between the presentation of the imperative stimulus and the release of the home key. Movement time (MT) was measured (in ms) as the time between releasing the home key and pressing the response key. Both speed and accuracy were emphasised. All errors were recorded: anticipations (RT less than or equal to 100 ms), long responses (RT greater than 3 s), errors of omission (failure to respond on go trials), errors of commission (responding on no-go trials) and partial errors (lifting the finger from the home key on a no-go trial, but correcting the mistake by replacing the finger on the home key). RT and MT from these trials were omitted, and the trials were repeated, that is, trials on which errors occurred were omitted from calculation of mean RTs, but to ensure equal number of trials across subjects any trials with errors were 'replaced' by administering an additional trial. There were two types of go no-go task.

5.2.2.1 Study 4

Figure 5.1 shows the stimuli for Study 4. Study 4 examined go no-go RTs as a function of increased complexity of the go no-go decision. The subject pressed down the home key to begin the trial and a fixation point, a small white cross, appeared in the centre of the screen. After a variable delay of 0.5, 1 or 2 seconds the fixation point disappeared and the imperative stimulus appeared in the centre of the screen and remained until the subject responded or for a maximum duration of 3 seconds. Each interval occurred with the same frequency. Stimuli consisted of two shapes (circles or squares) which varied in colour (yellow or purple) and size (small or large). Only one shape appeared on the screen at a time. The rule for response e.g. 'all stimuli' or 'large' or 'yellow square' or
'small purple circle' was written in capital letters above the fixation point and remained on the screen throughout the task.

Figure 5.1. The stimuli used in Study 4 for the go no-go reaction time task. Only one stimulus appeared on the screen for each trial.

Reaction times were measured under four different conditions: simple reaction time condition (SRT), in which subjects responded to each stimulus presented regardless of its nature and 3 choice reaction time conditions (CRT), in which the subjects responded on 80% of the trials (go) and withheld a response on 20% of the trials (no-go). The 3 CRT conditions were: CRT to one stimulus dimension (CRT1), where the subject responded to a specific colour, shape or size, e.g., respond to all 'yellow stimuli' and withhold response to all stimuli that are not yellow; CRT to two stimulus conditions (CRT2), where the subject responded to a specific combination of two features, e.g., 'large square'; CRT to three stimulus dimensions (CRT3), where the subject responded to a specific combination of three stimulus features, e.g., 'small purple circle'. In all conditions, a tone (800 Hz, 100 ms) was presented simultaneously with the stimulus. The order of the three CRT conditions (CRT1, CRT2, CRT3) was counter balanced in each group. Each CRT condition was preceded by an SRT condition to increase preparedness for responding prior to assessing response suppression on 20 percent of trials on the CRT conditions.
For each CRT condition, two sets of stimulus combinations, each containing 3 combinations of the relevant stimulus dimensions were used. For CRT1, in set 1, subjects responded to any stimulus that was ‘purple’, any stimulus that was a ‘circle’, and any stimulus that was ‘large’. For CRT1, in set 2, subjects responded to any stimulus that was ‘yellow’, any stimulus was a ‘square’, any stimulus that was ‘small’. For CRT2, in set 1, subjects responded to ‘large squares’, ‘small yellow’ stimuli, and ‘purple circles’. For CRT2, in set 2, subjects responded to ‘small circles’, ‘large purple’ stimuli, and ‘yellow squares’. For CRT3, in set 1, subjects responded ‘large yellow squares’, ‘small yellow circles’, and ‘large purple circles’. For CRT3, in set 2, subjects responded to ‘small yellow squares’, ‘large purple squares’, and ‘small purple circles’. The order of the two sets and the order of the three stimulus combinations in each set were counterbalanced across subjects in each group.

Each SRT run consisted of 40 trials and each CRT run had 80 correct responses (go trials) and 20 no-go trials.

5.2.2.2 Study 5

Study 5 was also a go no-go RT. In Study 5 the target go stimulus remained the same in each condition, so there was no variation in target selection. However the similarity of no-go stimuli to the target go stimuli varied across blocks, by varying the number of dimensions that they shared with the target stimulus. The nature of the stimuli used were different from those used in Study 4 to avoid confounds. The stimuli are presented in Figure 5.2. The target go stimulus was always an upper case ‘Q’ presented above the fixation cross. Only one stimulus was presented on each trial. The no-go stimuli (those stimuli for which the response was to be withheld) differed from
the target stimulus in terms of identity (letter, Q or R), case (upper or lower) and position (above or below fixation cross).

\[
\begin{array}{ccc}
Q & r & q, R \\
+ (\text{fixation cross}) & + & + \\
r & q, R & Q \\
\end{array}
\]

**Target** | **No-go stimulus**  
---|---
**CRT1** | **CRT2**  
**CRT3**  

Figure 5.2 The stimuli used in Study 5 for the go no-go reaction time task. Only one stimulus appeared on the screen for each trial.

In the SRT condition the upper case ‘Q’ appeared above the cross on each trial and the subject responded each time. The CRT tasks consisted of 80% ‘go’ trials and 20% ‘no-go’ trials. In CRT1 there was only one distracter, a lower case ‘r’ presented below the fixation cross which differed from the target stimulus on all three dimensions. In CRT2 each of the three no-go stimuli differed from the target go stimulus on two dimensions. The no-go stimuli were an upper case ‘R’ below the fixation cross, a lower case ‘q’ below the fixation cross, and a lower case ‘r’ above the fixation cross. In CRT3 each of the three no-go stimuli differed from the target go stimulus on one dimension only. The no-go stimuli were an upper case ‘Q’ below the fixation cross, a lower case ‘q’ above the fixation cross, and an upper case ‘R’ above the fixation cross.

In the SRT condition, stimulus presentation was continued until 80 correct responses, and in each of the CRT conditions 80 correct responses and 20 no-go trials were obtained. There was only one run of SRT which was presented first, followed by the 3
CRT tasks. The CRT conditions (CRT1, CRT2, CRT3) were counter balanced for order in each group.

5.2.2.3 Cognitive Tests

We also assessed the subjects on a number of cognitive tests that require volitional suppression of a habitual response.

**Word Fluency** (Benton, 1968) Three versions of this test were completed, each for 60 s. In the phonemic version, subjects were asked to produce words beginning with the letters F, A or S, excluding proper nouns and the same word with a different suffix each for 60 s. Two versions of the categorical word fluency were used. In the first, subjects were asked to produce nouns belonging to a specific category of animals for 60 s. In the final version, subjects were instructed to alternate between exemplars of two categories, boys names and fruit, again for 60 s. On each test, the score was the number of words generated correctly.

**Stroop Colour Word Naming Test** (Stroop, 1935) Four versions of this test were used, each consisting of 100 items. The first version required naming the colour of ink of colour words (green, blue, red) printed in incongruent ink. In the second version subjects named the colour of rectangles printed in different colour ink (green, blue, red). In the third version, subjects read the colour words printed in incongruent ink. In the fourth version, subjects read colour words printed in black ink. Subjects were instructed to perform each task as quickly as possibly and to correct any errors made. For each version the total time and total number of errors were recorded. The difference score between the first and second versions, takes motor speed into account and is a measure of the 'Stroop effect' i.e. the ability to maintain attention focused on one attribute of the colour words (ink) and ignore the other (meaning of colour words) while naming colours. The difference score between the third and fourth version is a measure of the
‘reverse Stroop’ effect, i.e., reading the words rather than naming colours with incongruent material.

**Hayling Test** (Burgess & Shallice, 1996) The test has two sections:

1. **Response Initiation**: subjects are instructed to provide an appropriate word to complete a sentence from which the last word is missing. For example: “the captain wanted to stay with the sinking……” for which the word “ship” would be an appropriate response. The initiation time, that is the mean response latency across all items is measured.

2. **Response suppression**: For each sentence read out, the subject is required to provide a word which makes no sense at all in the context of the sentence. For example, “Most cats see very well at …..”, for which “banana” would be an appropriate response. The suppression time, that is the mean response latency across all items is measured. In addition, for each item, an error score is derived by classifying the degree to which the subject’s response is related to the obvious high frequency response that the subject should suppress.

**Random Number Generation** Subjects were instructed to generate a series of 100 numbers in a random fashion. The analogy of picking numbers out of a hat was used to explain the concept of randomness to participants. Performance was paced with a ‘flashing’ (duration on screen=1000 ms) 1cm x 1 cm white square presented on the screen at the rate of once every 2 s. Subjects were instructed to synchronise their responses with the onset of the flashing square. The total time taken to generate 100 items was noted. We obtained several measures of randomness calculated using the procedures specified by Evans (1978), Rosenberg et al. (1990) and Ginsburg & Karpiuk (1994).

1. Count Scores are measures of seriation. We obtained count scores using the general method of Spatt & Goldenberg (1993). Count Score 1 (CS1), measures the
tendency to count in ascending or descending series in steps of 1. For example, 1-2-3 or 8-7-6-5-4. All count scores take the length of the series into account. In calculating the count scores, the sequence length is squared to give higher weights to runs of longer sequences. Therefore, these two examples would result in respective count scores of 4 (CS1=2²) and 16 (CS1=4²). Count Score 2 (CS2), measures the tendency to count in ascending or descending series in steps of 2, for example 2-4-6-8 or 7-5-3-1. The Total Count Score (CST) is a composite measure of the individual’s tendency to count in series ascending or descending in steps of 1 or 2. Individuals may have count scores that are lower than predicted from a random series if they are avoiding particular counting tendencies or they may have a score which is too high if they are unable to suppress particular counting tendencies.

2. Random Generation Index (RGI) is a first order measure which reflects any disproportion of digrams in the matrix adjusted for disproportions in the marginal cell frequencies. It varies between 0 and 1, and the higher the index the less random the series is.

We compared the measures of randomness obtained from our subjects with similar measures calculated for computer-generated pseudo-random series. A sample of one hundred, 100-item series were generated using the algorithm RAN1 from Sprott (1991).

5.2.3 Statistical methods
After checking the data for normality and outliers, two subjects’ data were removed as mentioned above. The RTs and MTs for the two no-go tasks were analysed separately using repeated measures analyses of variance (ANOVA). Large variance in the data of patient groups is a common finding in schizophrenia (Straube and Oades, 1992). In light of this, the relatively small sample sizes, and the nature of the group differences that were of primary interest, it was decided to compare only two groups at a time. For this reason the ANOVAS were run separately comparing the ‘high symptom’ patients
vs the 'low symptom' patients, the 'high symptom' patients vs the controls and the 'low symptom' patients vs the controls. The between subjects factor was Group ('high symptom' patients vs 'low symptom' patients, etc) and the within subject factors were Run (Run 1, Run 2, Run 3) for the SRT condition for Study 4, and Condition (CRT1, CRT2 or CRT3) for the CRT condition for Tasks 1 and 2. A one way ANOVA was used to analyse the data from the SRT condition of Study 5, with Group ('high symptom' patients vs 'low symptom' patients, etc) as the between subjects factor. In order to investigate the difference between increased choice complexity of target go stimuli and increased dimensional overlap of target go and no-go stimuli an ANOVA was run using the CRT data from both tasks. The three subject groups were used together in one analysis in order to determine the trend across all groups. The between subjects factor was group (controls, 'high symptom' patients, and 'low symptom' patients) and the between subjects factors were Task (Study 4 vs Study 5) and Condition (CRT1, CRT2 or CRT3). In order to investigate the difference between SRT conditions using stimulus invariance or stimulus variability across trials the mean SRTs of Study 4 and the SRTs of Study 5 were compared using an ANOVA. The between subjects factor was Group (controls, 'high symptom' patients, and 'low symptom' patients) and the within subjects factor was Task (Study 4 vs Study 5). Where necessary, to deal with violations of assumptions of sphericity, the Greenhouse-Geisser epsilon was used to adjust the degrees of freedom. Significant main effects or group interactions were followed up with paired or independent t-tests, as appropriate. Due to computer error, the data of one 'low symptom' patient is missing for the second run of the SRT for Study 4. One way ANOVAs were used to examine the group differences in the cognitive tests except on tests with different conditions (Hayling Test). For this, a repeated measures ANOVA was used with Group as the between subjects factor and Condition (initiation or suppression) as the within subjects factor.
5.3 Results

The two groups of patients and the normals did not differ in terms of male to female ratio ($x^2 = 0.49$, df = 2, $p > 0.05$), age [$F(2, 25) = 1.48$, $p > 0.05$] handedness, [$F(2, 25) = 2.66$, $p > 0.05$] (Oldfield, 1971) or estimates of ‘premorbid’ verbal IQ obtained from the National Adult Reading Test (NART, Nelson and Willison, 1991) [$F (2,25) = 0.46$, $p > 0.05$). The two groups did differ in terms of scores on the Beck Depression Inventory (BDI, Beck et al., 1961) [$F (2, 15) = 4.032$, $p < 0.05$]. Post hoc Tukey’s test showed that this difference was caused by higher depression scores for the ‘high symptom’ patients than the controls ($p < 0.05$) but no other groups differed significantly. The two patient groups did not differ in terms of chronicity, dose of neuroleptic medication or dose of anticholinergic medication ($p > 0.05$).

5.3.1 Study 4

5.3.1.1 Movement Time

A series of repeated measures ANOVA were carried out for the movement time (MT) data. Group (‘high symptom’ vs ‘low symptom’ patients, or ‘high symptom’ patients vs controls, or ‘low symptom’ patients vs controls) was the between subjects variable and Run (1, 2 or 3; SRT) or Condition (CRT1, CRT2 or CRT3) were the within subjects variables. The mean MTs and the results of the ANOVAS are presented in Table 5.3. There were no significant main effects of Run in the SRT ANOVAs or Condition in the CRT ANOVAS. There were no significant Group by Run or Group by Condition interactions in any of the ANOVAs for MTs. The ‘high symptom’ and ‘low symptom’ groups showed no significant differences in MT. Each patient group had significantly slower MTs for the SRT and CRT conditions than the control group ($p < 0.05$).
Table 5.3. The mean MTs and standard deviation (SD) for each group for Study 4 and the results of the ANOVAs on MTs. Where necessary, to deal with violations of assumptions of sphericity, the Greenhouse-Geisser epsilon was used to adjust the degrees of freedom. *(p ≤ 0.05)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean MT SRT (sd)</th>
<th>Mean MT CRT (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High patients</td>
<td>244.38 (52.43)</td>
<td>266.76 (55.16)</td>
</tr>
<tr>
<td>Low patients</td>
<td>255.89 (83.27)</td>
<td>276.19 (80.41)</td>
</tr>
<tr>
<td>Controls</td>
<td>196.28 (38.43)</td>
<td>192.63 (34.23)</td>
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</tbody>
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<table>
<thead>
<tr>
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<th>DF</th>
<th>F value</th>
<th>P value</th>
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<td>0.07</td>
<td>0.85</td>
</tr>
<tr>
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<td>Group x Run</td>
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<td>0.31</td>
<td>0.64</td>
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<td>Group</td>
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<tr>
<td>High Symptom Patients vs Controls</td>
<td>Condition</td>
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<tr>
<td>High Symptom Patients vs Controls</td>
<td>Group x Condition</td>
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<td>Group x Condition</td>
<td>2, 34</td>
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<td>Group</td>
<td>1, 17</td>
<td>13.26</td>
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<tr>
<td>Low Symptom Patients vs Controls</td>
<td>Run</td>
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<td>0.42</td>
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<tr>
<td>Low Symptom Patients vs Controls</td>
<td>Group x Run</td>
<td>2, 32</td>
<td>1.44</td>
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<td>Condition</td>
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<td>1.34</td>
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<td>Group</td>
<td>1, 17</td>
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5.3.1.2 Error Data

Very few errors of any type were made by the patients or normals. The median error data are shown in Table 5.4. A series of Kruskal-Wallis tests revealed no significant differences among the three groups in the number of anticipations, decision errors, or long responses in the SRT condition (p > 0.05). In the CRT condition there was a significant group difference in the number of errors of commission (going on a no-go)
(p = 0.02) and the number of anticipation errors (p = 0.02). Further analyses of these effects revealed that the patients in the ‘high symptom’ group made significantly more

Table 5.4. Median error values (and range) for Study 4 and Study 5. Values in marked boxes for the controls and the ‘low symptom’ patients differ significantly from the ‘high symptom’ patients (p < 0.05)

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticipation</th>
<th>Long Responses</th>
<th>Omission</th>
<th>Commission</th>
<th>Partial Errors</th>
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<tr>
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<td>0.00</td>
<td>0.00</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td></td>
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<td>(0.00-0.33)</td>
<td>(0.00-0.33)</td>
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</tr>
<tr>
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<td>0.00</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td>(0.00-0.33)</td>
<td>(0.00-0.00)</td>
<td>(0.00-0.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.00-1.00)</td>
<td>(0.00-0.33)</td>
<td>(0.00-0.00)</td>
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</tr>
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<td>CRT</td>
<td>Controls</td>
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<td></td>
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</tr>
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<tr>
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<td>/</td>
</tr>
<tr>
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<td>(0.00-0.00)</td>
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</tr>
<tr>
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<td>Controls</td>
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<tr>
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<tr>
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<td>1.33</td>
</tr>
<tr>
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<td>(0.00-2.00)</td>
<td>(0.67-2.33)</td>
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<tr>
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<td>0.67</td>
</tr>
<tr>
<td></td>
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<td>(0.00-0.00)</td>
<td>(0.00-0.67)</td>
<td>(0.00-0.33)</td>
<td>(0.33-6.00)</td>
</tr>
</tbody>
</table>
errors of commission than the 'low symptom' group (p = 0.007) and the normal controls (p = 0.05). The 'high symptom' group also made significantly more anticipation errors compared to the normal controls (p = 0.02) but this comparison did not reach significance between the two patient groups. There were no significant differences among the three groups in terms of the number of errors of omission, long responses or partial errors (p > 0.05).

5.3.1.3 SRT condition

The mean RTs for the SRT condition of each group are presented in Figure 5.3. An ANOVA examined the difference between the 'high symptom' patients and controls. The main effect of Group was significant [F(1,17) = 7.44, p = 0.01] with the 'high symptom' patients having slower RTs (406.62, sd = 82.49) than the controls (336.81, sd = 54.34). The main effect of Run was significant. Further investigation of this effect revealed that the RTs for Run 2 (359.56 ms, sd = 63.04) were significantly slower than those for Run 1 (330.58 ms, sd = 43.71) (t = 3.09, df = 18, p = 0.006) but no other Runs differed significantly. The Group x Run interaction was not significant.

In the ANOVA between the 'low symptom' patients and the controls the main effect of Group was not significant (p > 0.05) but the main effect of Run was significant [F(1, 21) = 4.81, p = 0.03]. Further analysis of this effect revealed that the RTs for Run 2 (359.56 ms, sd = 63.04) were significantly slower than the RTs for Run 1 (330.58 ms, sd = 43.70) but no other Runs differed significantly. The Group x Run interaction was not significant.
Figure 5.3 Mean RTs for the controls, 'low symptom' patients and 'high symptom' patients for Run 1 (white), Run 2 (grey) and Run 3 (black) for the SRT condition of Study 4.
A repeated measures ANOVA was carried out with Group (‘high symptom’ patients vs ‘low symptom’ patients) as the between subjects variable and Run (1,2 or 3) as the within subjects variable. The main effects of Group and Run were not significant, nor was the Group x Run interaction (p > 0.05).

5.3.1.4 CRT condition

The mean RTs for each group for the CRT condition are presented in Figure 5.4. An ANOVA between the ‘high symptom’ patients and the controls showed that the main effect of Group approached significance \([F(1, 17) = 4.16, p = 0.057]\) and the main effect of Condition reached significance \([F(2, 34) = 10.75, p < 0.001]\). Further analysis of the Condition effect revealed that the RTs for CRT3 were the fastest (459.84 ms, sd = 89.91) and were significantly faster than the RTs for CRT1 (475.63 ms, sd = 94.05) \((t = 5.52, df = 18, p = 0.02)\) and CRT2 (488.21, sd = 89.07) \((t = 3.87, df = 18, p = 0.001)\) while the RTs for CRT1 were faster than those for CRT2 \((t = 2.12, df = 18, p = 0.05)\). The Group x Condition interaction was not significant (p > 0.05).

In the ANOVA comparing the ‘low symptom’ patients and controls the main effect of Group was not significant (p > 0.05). The main effect of Condition was significant \([F(2, 34) = 7.736, p = 0.002]\). Further analysis revealed that once again across the two groups, the RTs for CRT3 were the fastest (449.89 ms, sd = 86.86) and were significantly faster than the RTs for CRT1 (464.68 ms, sd = 85.85) \((t = 2.49 df = 18, p = 0.02)\) and CRT2 (477.53 ms, sd = 81.58) \((t = 3.86, df = 18, p = 0.001)\) and the RTs for CRT1 were faster than those for CRT2 \((t = 2.17, df = 18, p = 0.04)\). The Group x Condition interaction was not significant.
Figure 5.4 Mean RTs for the controls, ‘low symptom’ patients and ‘high symptom’ patients for CRT 1 (white), CRT 2 (grey) and CRT 3 (black) for the CRT condition of Study 4.
A repeated measures ANOVA was carried out with Group ('high symptom' patients vs 'low symptom' patients) as the between subjects factor and Condition (CRT1, CRT2, CRT3) as the within subjects factor. The main effect Group was not significant (p > 0.05). The main effect of Condition was significant [F(2,24) = 3.59, p = 0.04]. Further analysis of this effect revealed that CRT 3 (492.43 ms, sd = 78.78) was significantly faster than CRT 2 (517.43 ms, sd = 72.07) (t = 2.43, df = 13, p = 0.03). The Group x Condition interaction was not significant (p > 0.05).

5.3.2 Study 5

5.3.2.1 Movement time

One way ANOVAs were carried out for the MT data for the SRT condition with Group ('high symptom' vs 'low symptom' patients, or 'high symptom' patients vs controls, or 'low symptom' patients vs controls) as the between subjects variable. Full results of the ANOVAS and the mean MTs are presented in Table 5.5. There was no significant difference between the MTs of the two patient groups (p > 0.05) but each patient group had significantly slower MTs than the controls (p > 0.05). Repeated measures ANOVAs were carried out for the movement time data for the CRT condition. Group ('high symptom' vs 'low symptom' patients, or 'high symptom' patients vs controls, or 'low symptom' patients vs controls) was the between subjects variable and Condition (CRT1, CRT2 or CRT3) was the within subjects variable. There were no significant main effects Condition in any of the analyses, nor were there any significant Group x Condition interactions (p > 0.05). There was no significant Group effect between the 'high symptom' patients and 'low symptom' patients (p > 0.05). Each patient group had significantly slower MTs for the CRT condition than the control group (p < 0.05).
5.3.2.2 Error data

Very few errors of any type were made by the patient groups or normals. The median error data are shown in Table 5.4. A series of Kruskal-Wallis tests revealed that there were no significant differences between the three groups in the number of anticipations, decision errors, or long responses in the SRT condition (p > 0.05). There were no significant differences among the three groups the number of errors of commission, omission, long responses or partial errors or anticipation errors in the CRT condition (p > 0.05).

Table 5.5. The mean MTs and standard deviation (SD) for each group for Study 5 and the results of the ANOVAs on MTs. Where necessary, to deal with violations of assumptions of sphericity, the Greenhouse-Geisser epsilon was used to adjust the degrees of freedom. *(p ≤ 0.05)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean MT SRT (sd)</th>
<th>Mean MT CRT (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High patients</td>
<td>252.71 (58.37)</td>
<td>298.67 (981.09)</td>
</tr>
<tr>
<td>Low patients</td>
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<tr>
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<table>
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5.3.2.3 SRT condition

The mean RTs for the SRT condition are presented in Figure 5.5. A one way ANOVA was run to compare the ‘high symptom’ patients vs controls. The main effect of Group was significant \[F(1,18) = 7.89, p = 0.01\] with the ‘high symptom’ patients having slower RTs (419.00ms, sd = 101.47) than the controls (312.33ms, sd = 65.10).

In the ANOVA between the ‘low symptom’ patients and the controls the main effect of Group was not significant \(p > 0.05\).

An ANOVA was carried out with Group (‘high symptom’ patients vs ‘low symptom’ patients) as the between subjects variable. The main effect of Group was not significant \(p > 0.05\).

5.3.2.4 CRT condition

The mean RTs for the CRT condition are presented in Figure 5.6. An ANOVA between the ‘high symptom’ patients and the controls showed that the main effect of Group approached significance \[F(1,17) = 3.96, p = 0.063\] and the main effect of Condition was significant \[F(1, 25) = 14.90, p < 0.001\]. Further analysis of the Condition effect revealed that the RTs for CRT3 (490.63 ms, sd = 92.71) were significantly slower than the RTs for CRT1 (451.68ms, sd = 97.91) \(t = 5.04, df = 18, p < 0.001\) and CRT 2 (467.58ms, sd = 92.56) \(t = 3.21, df = 18, p = 0.005\) while the RTs for CRT1 and CRT2 did not differ significantly \(p > 0.05\). The Group x Condition interaction was not significant \(p > 0.05\).
Figure 5.5 Mean RTs for the controls, 'low symptom' patients and 'high symptom' patients for the SRT condition of Study 5.
Figure 5.6 Mean RTs for the controls, 'low symptom' patients and 'high symptom' patients for CRT 1 (white), CRT 2 (grey) and CRT 3 (black) for the CRT condition of Study 5.
In the ANOVA comparing the ‘low symptom’ patients and controls the main effect of Group was not significant (p > 0.05). The main effect of Condition was significant [F(2, 34) = 14.92, p < 0.001]. Further analysis revealed that the RTs for CRT3 were significantly slower (479.11 ms, sd = 88.59) than the RTs for CRT1 (437.42 ms, sd = 87.36) (t = 5.93 df = 18, p < 0.001) and CRT2 (456.05 ms, sd = 83.91) (t = 3.21, df = 18, p = 0.005) and the RTs for CRT1 were faster than those for CRT2 (t = 2.11, df = 18, p = 0.05). The Group x Condition interaction was significant [F(2, 34) = 3.18, p = 0.05]. This interaction was analysed further. Independent t-tests revealed that the RTs for the ‘low symptom’ patients and the controls were not significantly different for CRT1, CRT2 or CRT3 (p > 0.05). However, a series of paired t-test revealed that the controls had significantly faster RTs for CRT1 (418.0 ms, sd = 91.2) than for CRT2 (450.0 ms, sd = 98.2) and CRT3 (462.6 ms, sd = 101.0) (p < 0.05) but the RTs for CRT2 and CRT3 did not differ significantly (p > 0.05). The ‘low symptom’ patients had significantly slower RTs for CRT3 (507.43 ms, sd = 58.07) compared to the RTs for CRT2 (466.43 ms, sd = 56.58) and CRT1 (470.41 ms, sd = 74.9) (p < 0.05) but the RTs for CRT1 and CRT2 did not differ significantly.

A repeated measures ANOVA was carried out with Group (‘high symptom’ patients vs ‘low symptom’ patients) as the between subjects factor and Condition (CRT1, CRT2, CRT2) as the within subjects factor. The main effect Group was not significant (p > 0.05). The main effect of Condition was significant [F(2,24) = 8.29, p = 0.002]. Further analysis of this effect revealed that the RTs for CRT 3 (529.14 ms, sd = 81.75) were significantly slower than the RTs for CRT 2 (503.50ms, sd = 84.44) (t = 2.90 df = 13, p = 0.01) and CRT 1 (487.79ms, sd = 79.55) (t = 3.73, d.f. = 13, p = 0.003). No other RTs differed significantly. The Group x Condition interaction was not significant (p > 0.05).
5.3.3 Comparison of Study 4 and Study 5

5.3.3.1 SRT conditions

A repeated measures ANOVA with a between subjects factor of Group (controls, ‘high symptom’ patients, and ‘low symptom’ patients) and a within subject factor of Task (Study 4 vs Study 5) was carried out to investigate the effects of stimulus invariance vs stimulus variation across trials on SRTs. The main effect of Group was significant \[ F(2,23) = 4.02, p = 0.03 \], but the main effect of Task and the Group x Task interaction failed to reach significance \( p > 0.05 \). Further investigation of the group effect revealed that across the two tasks the ‘high symptom’ patients had significantly slower SRTs (412.8ms) than the controls (324.6 ms) \( p < 0.05 \) but no other groups differed significantly \( p > 0.05 \).

5.3.3.2 CRT conditions

A repeated measures ANOVA was carried out comparing the 3 CRT conditions of the two tasks. The between subjects factor was Group (controls, ‘high symptom’ patients and ‘low symptom’ patients) and the within subjects factors were Task (Study 4 vs Study 5) and Condition (CRT1, CRT2, CRT3). The main effect of Condition \[ F(2, 23) = 4.00, p = 0.03 \] was significant with RTs for CRT 1 being significantly faster than RTs for CRT2 or CRT3 \( p > 0.05 \) across the two tasks, but the main effects Group and Task failed to reach significance \( p > 0.10 \). The interactions of Group x Task and Group x Condition failed to reach significance \( p > 0.10 \), but the interaction of Task x Condition was significant \[ F(2, 46) = 32.64, p < 0.001 \] and the Group x Task x Condition interaction approached significance \[ F(4, 46) = 2.206, p = 0.08 \].

Further analysis of the significant Task x Condition interaction revealed that RTs for CRT1 from Study 4 (484.9ms) were significantly slower than the RTs for CRT1 of Study 5 (455.6ms), and the RTs for CRT3 of Study 4 (464.7ms) were significantly
faster than the RTs for CRT3 of Study 5 (498.4), while the RTs for CRT2 did not differ significantly.

The Group x Task x Condition interaction was investigated further by comparing the mean RTs for CRT1, CRT2 and CRT3 collapsed across the 2 Tasks and by comparing the RTs for Study 4 and Study 5 collapsed across the three CRT conditions among the three groups. These analyses revealed that for Study 4 the 'high symptom' patients were significantly slower than the controls on all 3 CRT conditions (p < 0.05) whereas for Study 5, for all 3 conditions the groups approached significance (p = 0.06). The 'high symptom' patients had significantly slower RTs than the controls for CRT1 and CRT3 (p < 0.05) and the difference approached significance for CRT2 (p = 0.06) across the two tasks. The RTs of the 'low symptom' patients did not differ significantly from the controls or the 'high symptom patients (p> 0.10) for either Study 4 or Study 5.

5.3.4 The Results of the Cognitive Testing

The Hayling Test was analysed using an ANOVA with Group ('high symptom' patients and controls) as the between subjects factor and Condition (response initiation vs response suppression) as the within subjects factor. The main effect of Group was significant [F(1,17) = 8.24, p = 0.01], the main effect of Condition was significant [F(1, 17) = 20.29, p < 0.001] and the Group x Condition interaction was significant [F(1,17) = 5.65, p = 0.03]. The mean response times of both groups for the two conditions are presented in Figure 5.7. Further examination of the interaction effect revealed that the response initiation times did not differ significantly between the 'high symptom' patients (18.78ms, sd=4.98) and the controls (15.37ms, sd=4.53)(p>0.05),

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Figure 5.7. Mean response times for the initiation condition (white) and the suppression condition (grey) of the controls and ‘high symptom’ patients in the Hayling test.
but the 'high symptom' patients had significantly slower response suppression times (62.75 ms, sd = 38.66) than the controls (28.97 ms, sd = 16.79) (t = 2.66, df = 17, p = 0.02). The two groups did not differ significantly in terms of errors made on the Hayling test (p > 0.05). The 'high symptom' patients and controls did not differ significantly on any measures of random number generation, the Stroop or reverse Stroop effects (p > 0.05). The control subjects generated significantly more words for the alternating word fluency task [F(1, 12) = 6.332, p = 0.02] but the two groups did not differ in terms of first letter or single category word fluency (p > 0.05).

In the analysis of the Hayling Test for the 'low symptom' patients and controls, the main effect of Group was significant [F(1,17) = 4.92, p = 0.04], as patients were slower to respond than controls. The main effect of Condition was significant [F(1, 17) = 14.63, p = 0.001] with response initiation times (18.71ms, sd = 7.29) being faster than response suppression times (36.21ms, sd = 24.81). The Group x Condition interaction was not significant (p > 0.05). The two groups did not differ significantly in terms of errors made on the Hayling test (p > 0.05). The 'low symptom' patients and controls did not differ significantly on any measures of random number generation (p > 0.05). The control subjects generated more words for the alternating word fluency task than the 'low symptom' patients [F(1, 17) = 4.82, p = 0.04] but the two groups did not differ in terms of first letter or single category word fluency (p > 0.05). The two patient groups did not differ in the Stroop effect or the reverse Stroop effect or the number of errors made on the two interference conditions (p < 0.05).

In the analysis of the Hayling Test for the 'high symptom' patients and 'low symptom' patients the main effects of Group was not significant [F(1,12) = 0.19, p > 0.05] but the main effect of Condition was significant [F(1, 12) = 12.47, p = 0.004]. Further analysis
of this main effect revealed that response times to the response suppression condition (55.68 ms, sd = 35.02) were longer than the response initiation condition (21.62 ms, sd = 6.94). The Group x Condition interaction was not significant. The two groups of patients did not differ in the number of errors on the Hayling (p > 0.05). The two patient groups did not differ significantly on any measures of random number generation (p > 0.05), first letter, single category or alternating category word fluency, the Stroop or reverse Stroop effects (P > 0.05).

5.3.5 Correlational Analysis
Correlational analyses were carried out to examine the relationship between medication level, RTs and errors using Pearson’s correlation coefficients for the patients with schizophrenia. There was a positive correlation between level of anticholinergic medication and the number of anticipation errors in the CRT condition in Study 4 (r = 0.63, p = 0.02). There was a positive correlation between level of neuroleptic medication and the number of long response errors in the CRT condition in Study 4 (r = 0.79, df = 14, p = 0.01).

Correlational analyses were carried out on all subjects examining the relationship between results on the cognitive tests and RTs and errors using Pearson’s correlation coefficients. Word fluency was negatively correlated with number of errors for the CRT condition, Study 5, suggesting that higher word fluency scores were associated with fewer errors (Mean score for FAS and anticipation errors, r = -0.49, p = 0.01; mean FAS score and errors of omission, r = -0.40, p = 0.04; alternating category and anticipation errors, r = -0.40, p = 0.04). The Stroop effect and errors of omission on SRT in Study 4 were positively correlated (r = 0.52, p = 0.01). The reverse Stroop effect was positively correlated with RTs in the SRT and CRT conditions for both tasks (range of r: 0.44 to 0.63, p < 0.05), that is greater reverse Stroop effect was linked with
slower reaction times. The count score 1 in the random number generation task was positively correlated with anticipation errors for the SRT condition of Study 4 (r = 0.58, p = 0.003).

Correlational analyses were carried out to examine the relationship between the individual symptoms as rated by the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Signs (SANS), RT and errors using Pearson’s correlation coefficients. The significant correlations are presented in Table 5.5. The p values were adjusted for the number of correlations (330) by carrying out a Bonferroni correction. After this adjustment there were no significant correlations remaining.

There is a possibility that factors such as levels of antipsychotic medication, anticholinergic medication, depression, or cognitive deficits which have been shown to differ among patients with schizophrenia, could confound the findings of correlational analyses. Therefore, Pearson’s Partial Correlations were run controlling for dose of neuroleptic, dose of anticholinergic, BDI score, and Mini Mental score. The significant results are presented in Table 5.6. After the Bonferroni correction for number of correlations (300) there were no significant correlations.
Table 5.6 Pearson's correlations between measures of reaction time and the individual symptom ratings of the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative signs (SANS) depression as rated on the Beck Depression Inventory (BDI). The r and p values are given. Only coefficients with p < 0.05 are presented. CRT = choice reaction time, RT = reaction time.

<table>
<thead>
<tr>
<th>Study 4</th>
<th>SAPS SANS</th>
<th>BDI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hallucination</td>
<td>Thought</td>
</tr>
<tr>
<td></td>
<td>Disorder</td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>r = 0.56</td>
<td>r = 0.54</td>
</tr>
<tr>
<td>anticipation</td>
<td>p = 0.04</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>errors</td>
<td>CRT partial</td>
<td>r = -0.63</td>
</tr>
<tr>
<td>errors</td>
<td>p = 0.02</td>
<td></td>
</tr>
<tr>
<td>Study 5</td>
<td>CRT2</td>
<td>r = 0.62</td>
</tr>
<tr>
<td></td>
<td>p = 0.03</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>CRT3</td>
<td>r = 0.56</td>
<td>p = 0.04</td>
</tr>
<tr>
<td>CRT long</td>
<td>r = 0.62</td>
<td>r = 0.76</td>
</tr>
<tr>
<td>responses</td>
<td>p = 0.02</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>
Table 5.7 Pearson's Partial correlations between measures of reaction time and the individual symptom ratings of the Schedule for the Assessment of Positive Symptoms (SAPS) and the Schedule for the Assessment of Negative signs (SANS) controlling for levels of medication, depression, and Mini Mental score. The r and p values are given. Only coefficients with p < 0.05 are presented. CRT = choice reaction time, RT = reaction time.

<table>
<thead>
<tr>
<th>Study 4</th>
<th>SANS</th>
<th>SAPS</th>
<th>Anhedonia</th>
<th>Avolition</th>
</tr>
</thead>
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<tr>
<td>CRT Partial Errors</td>
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<td>d.f. = 7</td>
<td>p = 0.04</td>
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</table>

<table>
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<tr>
<th>Study 5</th>
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<th>SAPS</th>
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<th>Avolition</th>
</tr>
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<td>RT CRT2</td>
<td>r = 0.66</td>
<td>d.f. = 7</td>
<td>p &lt; 0.05</td>
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</tr>
<tr>
<td>RT CRT3</td>
<td>r = 0.74</td>
<td>d.f. = 7</td>
<td>p = 0.02</td>
<td></td>
</tr>
<tr>
<td>CRT Long Responses</td>
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<td>d.f. = 7</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>CRT Long Responses</td>
<td>r = 0.90</td>
<td>d.f. = 7</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>
5.4 Discussion

The patients with 'high symptoms' had significantly slower RTs than the controls in SRT conditions of both studies, however, group differences in RTs of the CRT conditions only approached significance. In Study 4, the RTs for both patient groups gradually became slower across runs, while the controls were slightly faster for Run 3 compared to Run 2, but these group differences did not reach significance. There were no Group differences between the 'low symptom' patients and the controls for either the SRT or the CRT conditions of either study, however there was an interesting Group x Condition interaction in Study 5. The controls showed greater slowing between CRT1 and CRT2 than between CRT2 and CRT3, whereas the RTs of 'low symptom' patients did not differ at all between CRT1 and CRT2 and slowed greatly for CRT3.

The two groups of patients did not differ on MT. MTs were slower for the both patient groups than for the controls in all conditions, but there were no differential effects of condition on MT, suggesting that decision making had occurred prior to movement initiation. There were no group by condition interactions which suggests that the conditions did not affect MTs differently in the two groups.

The patients with 'high symptoms' had more commission errors than the 'low symptom' patients and the controls and had more anticipation errors than the controls in the CRT condition for Study 4. This failure of response suppression (Nideffer et al., 1971; Fukushima et al., 1994) has been reported in schizophrenia in other tasks. There were no other differences between the two groups in terms of errors. One previous study assessed patients with schizophrenia on a go no-go RT task (Klein et al., 1996). As expected the patients had slower RTs than normal controls, but the patients did not have an increased error rate compared to controls. Errors were defined as trials on
which the subject used the incorrect hand in a left-right choice reaction time go-trial, failed to respond in a go-trial, or pressed a button during a no-go trial and these trials were removed. This led to 7% of go trials and 1% of false alarms on no-go trials being rejected in both groups. Unfortunately there is no mention of other statistical analysis of these error data.

The final point to consider is the possibility that the RTs of the patients and controls were subject to differential slowing as a result of fatigue or differential speeding associated with practice across the session. The repeated runs of SRT in Study 4 allows examination of such possible differential fatigue and practice effects across the two groups. Despite some non-significant slowing of SRTs from the first to the third run for the patients which was not evident for the controls, the Group x Run interaction was not significant, thus showing that the RTs of the patients and controls were not subject to such differential fatigue or practice effects across the session. It is of interest, that in Parkinson's disease, another disorder in which slowness of movement initiation and execution has been considered to reflect impairment of willed action (Jahanshahi & Frith, 1998), practice has been shown to be associated with greater speeding of SRT relative to age-matched normals (Worthingham and Stelmach 1990), suggesting that with practice patients are more likely to engage in the optional and volitional preprogramming involved in RTs. The present results suggest that the SRTs of patients with schizophrenia were not subject to such differential practice effects and that the SRT of the 'high symptom' patients were significantly slower than the controls across all three runs.

5.4.1 Group differences in SRT Conditions
The patients with 'high symptoms' had slower RTs than the controls in the SRT conditions of both studies. In both SRT conditions, the nature of the response was
invariant and involved releasing a 'home' button. The subjects were required to respond to all stimuli across trials in a block. In Study 5, the string of stimuli in a block were invariant (Q above fixation point), while in Study 4, the specific nature of the stimuli changed across trials in an SRT block. Nevertheless, given the invariant nature of the *response* and the instructions to respond to all stimuli, the response could be preprogrammed prior to stimulus onset. One interpretation of the significant slowness of SRTs for both Study 4 and 5 for the patients with 'high symptoms' in conjunction with normal CRTs is that these patients were failing to engage in the optional and volitional preprogramming of the response prior to presentation of the stimulus. The patients with 'low symptoms', however, did not differ from the controls on either of the SRT conditions.

The SRT condition of Study 5 differed from the SRT condition of Study 4 in one fundamental way. In Study 5 the stimulus was invariant. In Study 4, subjects responded to eight different types of compound stimuli. It would be expected that the invariant nature of the stimulus in Study 5 would allow development of 'set' to a greater extent than the variant stimuli of Study 4, yet these differences although in the right direction were not statistically significant for either the patients or controls.

5.4.2 The effect of complexity of go no-go decision-making and dimensional overlap of target/non-target stimuli on go no-go CRTs

5.4.2.1 Study 4

In Study 4, based on the results of previous studies (Cooper et al, 1994) it was expected that RTs would become slower from CRT1 to CRT2 and from CRT2 to CRT3, as the decision on 'go' trials was based on the conjunction of an increasing number of stimulus features (1 to 3). Contrary to expectation, RTs were in fact fastest for CRT3 compared to CRT2 and CRT1, for both the controls and patients. In CRT3 of Study 4,
subjects have to respond to three features of a compound stimulus: size, colour and shape, by responding only to a 'large yellow circle' for instance. The finding that RTs for CRT 3 were faster than RTs for CRT2 or CRT1 conditions suggests that instead of being the most difficult condition in terms of response selection, CRT3 is in fact the easiest. There are two possible reasons for this. First, in CRT3 of Study 4 subjects are required to only respond to a single target stimulus e.g. 'large yellow circle' as noted above. In contrast, in the CRT2 condition, there are two valid stimuli for example with 'yellow circle' as the target there are two possible target stimuli large yellow circles and small yellow circles. In the CRT1 condition, there are four possible target stimuli, for example, if one were responding to 'large' stimuli the decision to move would be made if the stimulus was a 'large yellow square', 'large purple square', 'large yellow circle', or a 'large purple circle', hence there were four valid stimuli. The fact that RTs increase as the number of stimulus or response alternatives increase is a most widely replicated finding, a relationship which is expressed by the Hick-Hyman law (Hick, 1952; Hyman, 1953). Thus, in line with the Hick-Hyman law, RTs were fastest for the CRT3 condition because this involved a single valid stimulus across trials compared to 2 and 4 respectively for CRT2 and CRT1. The second possibility related to the first is that as a result of a single compared to 2 or 4 stimulus alternatives, subjects had fewer examplars of the target 'go' stimulus to hold 'on line' across trials in a block in CRT3, which would account for the faster RTs. Also, with a single stimulus alternative it is easier to establish and maintain 'set' that is a state of preparedness or readiness to respond than with 2 or 4 possible stimulus alternatives.

The design of the go no-go RT of Study 4 was similar to that used by Cooper et al. (1994) in their study with patients with Parkinson's disease. Unlike the present results, they found that the go no-go CRTs of patients with Parkinson's disease and the normal
controls increased as stimulus complexity increased. However, there were a number of procedural differences between the Cooper et al., and the present study. First, instead of size as a feature of the compound stimulus, Cooper et al., had coloured circles and squares presented in conjunction with either a high or low-pitched tone. This combination of auditory with visual features may have meant that stimulus discrimination and hence the go no-go decision may have been more difficult in the study of Cooper et al. (1994) than in our study which simply relied on the visual features of compound stimuli. One indication of this would have been if the CRTs were slower in the Cooper et al. study than in the present study. However, the fact that that controls in their study were older than the controls in the present sample, means that a direct comparison of CRTs is not valid. A second important procedural difference is that in the study by Cooper et al. (1994) the response criteria in the CRT conditions changed after the subject made 10 correct responses compared to the present study where response criteria changed after 80 correct responses. Once again, this procedural difference may have made Study 4 easier than the analogous version used by Cooper and colleagues.

In Study 4, another aspect of the procedure used may have inadvertently influenced task difficulty and may help explain why differential effects were not obtained for the patients and controls. On each trial, the specific nature of the target stimulus, for example ‘large yellow circle’ in the CRT3 condition, or ‘yellow circle’ in the CRT2 condition was presented above the stimulus. Provision of this external cue informing subjects of the relevant stimulus dimensions may have reduced the working memory load of Study 4. In light of deficits shown by patients with schizophrenia on tests with a working memory component such as the Wisconsin Card Sorting Test (Nathaniel-James et al., 1996), it would be expected that the patients would show greater deficits in the
absence of such a cue, which would have necessitated relying on working memory across trials in a block.

5.4.2.2 Study 5

For Study 5, as expected, the RTs increased across the three CRT conditions for the controls and patient groups. Thus, as the dimensional overlap of no-go ‘distractor’ stimuli with the target ‘go’ stimulus increased, RTs increased. The only exception was found for the patients with ‘low symptoms’ for whom RTs did not increase between CRT1 and CRT2, but did increase for CRT3. The controls were significantly faster than the ‘high symptom’ patients but the two groups did not differ in their RTs across the three conditions. In contrast, the controls and ‘low symptom’ patients differed in terms of the effect of CRT condition on RTs. While the controls had significantly slower RTs in CRT2 and CRT3 compared to CRT1, the ‘low symptom’ patients showed no significant difference between CRT1 and CRT2 and but were significantly slower on CRT3 than the other two conditions. This suggests that for the controls, the greatest relative prolongation of RTs on the go trials was produced when the number of non-target no-go stimuli increased from one non-target no-go stimulus (always ‘r’ below fixation) in the CRT1 condition to three non-target no-go stimuli in the CRT2 and CRT3 conditions. In contrast, for the ‘low symptom’ patients, a significant increase in go RTs was obtained in Study 5 when the non-target no-go stimuli had the greatest dimensional overlap with the target go stimulus and differed from it only in terms of one dimension either identity, case or location; but not when the non-target and target stimuli differed in terms of two (CRT2) or three (CRT3) dimensions.

5.4.3 Group differences on cognitive tests requiring response suppression

Significant differences between the patients and controls were found on specific aspects of the cognitive tasks. Both patient groups had slower response times on the Hayling
test compared to the controls and the ‘high symptom’ group had significantly longer response times for the response suppression condition compared to the response initiation condition than the controls. None of the groups differed significantly on the number of errors made on the Hayling test. These results lend some support to previous studies which have found impaired performance on the Hayling test in patients with schizophrenia (Nathaniel-James and Frith, 1996). Both patient groups produced significantly fewer words in the alternating word fluency task compared to the controls. This deficit on tests of word fluency also replicates previous findings in schizophrenia (Liddle and Morris, 1991, Frith 1992, Beatty et al., 1993, Crawford et al., 1993, Abbruzzese et al, 1995). However, unlike previous studies reporting deficits on the Stroop (Mahurin et al., 1998; Liddle and Morris, 1991, Jaquet et al., 1997) or random number generation (Rosenberg et al., 1990) in patients with schizophrenia, neither of the two patient groups differed significantly from the controls on the Stroop or RNG tasks. The absence of such significant group differences may partly relate to the fact that the present sample were not highly symptomatic at the time of study, with only 7 of the 14 patients having relatively high positive and negative ratings.

More importantly in relation to the aims of the present study was the finding that performance on the cognitive tasks requiring suppression of habitual responses correlated with performance on the go no-go tasks. Word fluency was negatively associated with errors in the CRT condition of Study 5, suggesting that poorer word fluency correlated with higher errors on the go no-go task. A larger ‘Stroop’ effect, that is greater susceptibility to interference from the colour words was associated with more omission errors in the SRT condition of Study 4. Higher count score 1, indicative of a failure to suppress habitual counting during random number generation was associated with greater anticipation errors in the SRT condition of Study 4. These correlations
suggest that the go no-go tasks and the cognitive tasks may both be tapping some common ability to inhibit or suppress inappropriate responses for selection or release of the appropriate response.

Servan-Schreiber et al. (1996) used a variation of the CPT in patients with schizophrenia. They varied the interstimulus interval (ISI) between 750 ms and 5 s and the percentage of targets to non-targets to 80% to 20%. The rule was to respond when the letter X appeared, if it was preceded by an A (AX). On 10% of the trials X appeared, preceded by a different letter (BX) and in 10% of the trials A appeared, followed by a different letter (AY). The authors propose that the two cognitive impairments reported in schizophrenia, dysfunction of working memory (Weinberger et al., 1986) and impaired inhibition (Manschreck et al., 1988), can be explained by a single mechanism - an impairment in maintaining contextual information over time. According to this model, patients with schizophrenia with a mild impairment in maintaining contextual information would show an increase in BX errors on long ISIs, reflecting a working memory deficit, whereas patients with severe impairments in maintaining contextual information would show an increase in AY errors for the short ISIs, reflecting impaired inhibition. Unmedicated patients tested during their first episode exhibited working memory impairments, whereas the unmedicated ‘multi-episode’ patients (those recently admitted who had a long history of relapse) exhibited impaired inhibition. Other reports of intact inhibition but impaired memory in first episode schizophrenia has been reported (Hutton et al., 1998). These findings and the results of the current study suggest that impaired performance on no-go tasks may be dependent on duration of illness and symptom severity. In the present study, significant group differences in RTs were found between patients with high positive and high negative symptoms relative to controls, while differential effects of condition on RTs
was seen for patients with high negative signs relative to normals. The effect of symptom severity is clearly an issue that requires further investigation using a larger number of patients with more severe symptom ratings. For example, it would be interesting to compare patients with very high ratings of positive symptoms with patients with very high ratings of negative signs and also to compare a large group of patients with very high symptom ratings to a group of patients with very low symptom ratings.

Another possible explanation for the lack of major differences between the patients and controls may relate to the ratio of go to no-go trials. As we were interested in a failure of inhibition in schizophrenia, the current study was designed to increase the tendency to make errors of commission. Thus an 80% go to 20% no-go ratio was chosen, based on the rationale that the increased preparedness to respond on 80% of the trials should promote high errors of commission. However, it is also possible that with only 20% of the trials requiring response inhibition, sufficient sampling of the no-go performance was not undertaken. In effect, if the key factor determining the success or failure of response inhibition is the degree of uncertainty, a task with a 50/50 ration of go to go-no trials would be optimal. This issue can be examined more fully in future studies by systematic variation of the proportion of go to no-go trials across blocks from 80/20, to 50/50 to 20/80 for example.
CHAPTER 6

Study 6: Reduced negative priming does indicate reduced cognitive inhibition in schizophrenia

6.1 Introduction

Having shown that patients with schizophrenia have some impairments in willed initiation and suppression of action, the aim of Study six was to investigate the impairment in inhibition further. One feature of the attentional problems in schizophrenia is the greater distractibility of these patients in the presence of irrelevant information, for example as shown in dichotic shadowing tasks (Spring, 1985). Inadequate functioning of inhibitory attentional processes has been proposed as a mechanism of this increased distractibility in schizophrenia. The inability of patients with schizophrenia to maintain attentional set as demonstrated by the ‘cross over’ RT effect (Shakow, 1962), and the demonstration of abnormal recognition thresholds in a priming paradigm (Bullen and Hemsley, 1987) have all been considered evidence for ‘weakened inhibition’ in schizophrenia. Other empirical support for failure of inhibitory processes in schizophrenia exists. Inhibition of irrelevant information at an early stage of information processing has been termed ‘sensory gating’ (McDowd et al., 1993). One paradigm used to measure sensory gating is prepulse inhibition (PPI) which focuses on the eyeblink component of the startle reflex. Normally when the startle stimulus is preceded by a warning signal (prepulse), the eyeblink in the startle reflex is reduced, especially if the subject is told to attend to the prepulse (See McDowd et al., 1993 for a review). Patients with schizophrenia have reduced PPI (Braff et al., 1992; Grillon et al., 1992). Similar inhibition impairments are seen in latent inhibition (Baruch et al, 1988) and the Kamin blocking effect (Jones et al., 1992) as discussed in
Chapter 1. In the antisaccade task subjects are required to move their eyes to the opposite direction of a target. Patients with schizophrenia have difficulty suppressing eye movements to the target and therefore make more incorrect (towards the target) eye movements (Fukushima et al., 1994).

Another way to test inhibitory processes is by using the negative priming paradigm. First described by Tipper (1985) negative priming refers to the slowing of reaction times that occurs when an ignored distractor stimulus in a first trial becomes the target stimulus in the subsequent trial. Generally, in a negative priming experiment RTs are measured for response to two displays presented in quick succession. The first display is called the prime, the second display is called the probe and both displays consists of a target and a distractor. There are two types of probes; ignored repetition and control. In the ignored repetition probe, the target is the same as the distractor of the prime. In the control probe, the target is different than the distractor in the prime. Negative priming is considered to have occurred if RT is slower in the ignored repetition condition than in the control condition. Later studies investigated spatial negative priming (Tipper et al., 1990). In these, the delayed RTs occurred when the probe target shared the same location as the prime distractor (ignored repetition) compared to the control condition where the probe target was presented in a previously vacant location.

Normal control subjects show delayed reaction times in the ignored repetition condition presumably because the active task of ignoring the stimulus in the first trial is carried into the second trial and inhibits the subject's response to this previously ignored stimulus (Tipper and Cranston, 1985; Tipper et al., 1991). Patients with schizophrenia do not show a significantly increased RT when a previously ignored stimulus becomes the target (Park et al., 1996; Williams, 1996; Beech et al., 1989; Laplante et al., 1992;
David, 1995; Salo et al., 1996), in line with the proposal of a breakdown of inhibitory processes (Frith, 1979).

The most widely accepted view of negative priming is that it represents the operation of inhibitory mechanisms in selective attention such that the distracting stimuli are selectively inhibited during the prime trials (e.g., Tipper 1985). There have been other accounts besides this selective inhibition to explain the phenomenon of negative priming. According to the ‘episodic retrieval’ account, the ignored distractor in the prime 'episode' is encoded with a 'to-be-ignored' tag and as a result, responses to previously ignored probes are slowed by the automatic retrieval of the prior episode along with the to-be-ignored tag (Neill and Valdes, 1992). Recently Milliken et al. (1998) have suggested a 'temporal discrimination' account of negative priming. They propose that slowed RTs result from ambiguity in the categorisation of the probe stimulus as 'old' or 'new' relative to the prime. On ignored repetition trials, the familiarity of the probe target which has been previously seen as the ignored distractor on the prime trial, rules out its classification as 'new' and yet is insufficient to allow its consideration as 'old'. This ambiguity in the temporal discrimination process is considered to underlie the delayed RTs on ignored repetition trials.

From a different perspective, Park and Kanwisher (1994) have suggested the interpretation of previous spatial negative priming studies as reflecting the operation of inhibitory processes may actually be a result of perceptual mismatch rather than indicative of active inhibition. Because the probe target differs from the prime distractor in some form, either in colour, identity or size, the hesitation and hence prolonged RT shown by normals in responding on the probe trial may have nothing to do with reduced inhibition but instead reflect the detection of the perceptual mismatch.
This point has been addressed by Milliken et al. (1994), Tipper et al. (1995) and Watson and Tipper (1997). Milliken et al. (1994) confirmed that perceptual mismatch can contribute to negative priming in some situations. In a series of three experiments Tipper et al. (1995) found a spatial negative priming effect in normals whether the prime distractor and target probe matched or mismatched in terms of size or identity. However, the spatial negative priming effect was smaller when the colour of the prime distractor and target probe matched, than when they mismatched. Therefore, Tipper et al. (1995) concluded that perceptual mismatch and distractor inhibition produce additive effects on RT. In a subsequent study Watson and Tipper (1997) found reduced negative priming in schizotypal subjects using a negative priming paradigm on which there was no perceptual mismatch.

The previous studies examining negative priming in schizophrenia are presented in Table 6.1. The majority of the studies which have examined negative priming in patients with schizophrenia used Stroop stimuli in which the stimuli have a colour mismatch confound, because the prime distractor and the probe target were different colours (Beech et al., 1989; Laplante et al., 1992; David, 1995; Salo et al., 1996, Salo et al., 1997). The two studies that examined spatial negative priming in schizophrenia (Park et al., 1996; McDowd et al., 1993) with a task other than the Stroop used an X-O paradigm which also involves an identity mismatch between the prime distractor and probe target. This means that reduced negative priming in schizophrenia in these studies cannot unequivocally be attributed to a failure of inhibition and instead may indicate these patients' insensitivity to the effects of perceptual mismatch between stimuli due to poor episodic encoding or retrieval for prime/probe comparisons relative to normal subjects. Although inhibitory deficits have been demonstrated clearly from other paradigms, studies using negative priming tasks lead to ambiguous interpretations,
<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients with schizophrenia</th>
<th>Control group</th>
<th>Results</th>
<th>Perceptual mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beech et al.,</td>
<td>18 patients with schizophrenia</td>
<td>18 psychiatric patients with major psychotic illness, 12 with neurotic symptoms, 6 with personality disorder</td>
<td>Reduced NP in patients with schizophrenia</td>
<td>Yes - Colour – Stroop colour words</td>
</tr>
<tr>
<td>1989</td>
<td></td>
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<tr>
<td>Laplante et al.,</td>
<td>8 positive and 10 negative schizophrenia patients</td>
<td>21 psychiatric patients with major depression</td>
<td>Reduced NP in patients with schizophrenia, greater deficit in patients with negative schizophrenia</td>
<td>Yes - Colour – Stroop colour words</td>
</tr>
<tr>
<td>1992</td>
<td></td>
<td>35 normal controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDowd et al.,</td>
<td>8 older patients with schizophrenia (mean age = 54 years)</td>
<td>10 older controls (mean age = 66 years)</td>
<td>Reduced NP in patients with schizophrenia, greatest NP in young controls</td>
<td>Yes - Identity- Target = O Distractor= +</td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td>10 young controls</td>
<td></td>
<td></td>
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<tr>
<td>David, 1995</td>
<td>46 patients</td>
<td>22 patients with either bipolar affective disorder or major depression</td>
<td>Net priming effect (negative priming RT – positive priming RT) only significant in normal controls</td>
<td>Yes - Colour – Stroop colour words</td>
</tr>
<tr>
<td></td>
<td>21 acute</td>
<td>16 normal controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 chronic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 in remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park et al., 1996</td>
<td>18 chronic patients</td>
<td>28 normal controls</td>
<td>Acute patients showed reduced NP. Chronic patients showed intact NP</td>
<td>Yes - Identity- Target = O Distractor= +</td>
</tr>
<tr>
<td></td>
<td>19 acute patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salo et al., 1996</td>
<td>12 patients with chronic schizophrenia withdrawn from antipsychotic medication for at least 2 weeks</td>
<td>16 normal controls</td>
<td>Patients showed reduced NP</td>
<td>Yes - Colour – Stroop colour words</td>
</tr>
</tbody>
</table>

Table 6.1. Previous studies of negative priming (NP) in patients with schizophrenia
<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients with schizophrenia</th>
<th>Control group</th>
<th>Results</th>
<th>Perceptual mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams, 1996</td>
<td>34 patients with schizophrenia</td>
<td>None</td>
<td>Subgroups of disorganisation, reality distortion and episodic patients showed reduced NP. Subgroup of patients with psychomotor poverty showed normal NP</td>
<td>Yes - Colour – words were presented in red or green</td>
</tr>
<tr>
<td>Salo et al., 1997</td>
<td>14 patients withdrawn from medication for at least 2 weeks 10 medicated patients</td>
<td>16 controls</td>
<td>Medicated patients and controls showed similar NP. Patients withdrawn from medication showed a lack of NP</td>
<td>Yes - Colour – Stroop colour words and animal names in coloured ink</td>
</tr>
</tbody>
</table>
which are not clearly attributable to reduced inhibitory effects. The aim of this study is to examine the spatial negative priming effect in schizophrenia using a new paradigm that allows the effects of perceptual mismatch on RT to be considered independently of any spatial negative priming effects. We predicted that patients with schizophrenia would show significantly less negative priming, both in conditions where the prime distractor and probe target matched or had a perceptual mismatch.

6.2 Method

6.2.1 Subjects
Table 6.2 lists the characteristics of the subject groups. Fourteen patients with schizophrenia and 17 normals (3 female, 14 male) took part in the study. Two patients were multivariate outliers and had RTs which were extreme outliers compared to group means, one patient on 2 of the 4 and one patient on all 4 measures of interest (C+, C-, L+ L-). These two cases were therefore excluded. The remaining patients (2 female, 10 male) and normals did not differ in terms of male to female ratio ($x^2 = 0.11$, df = 1, $p = 0.74$), age ($t = 1.30$, df = 27, $p = 0.20$) handedness, ($t = 1.56$, df = 27, $p = 0.13$) or estimates of 'premorbid' verbal IQ obtained from the National Adult Reading Test (NART, Nelson and Willison, 1991) ($t = 1.45$, df = 22, $p = 0.16$). The two groups did differ in terms of scores on the Beck Depression Inventory (BDI, Beck et al., 1961) with the patients having higher scores than the normals ($t = 2.38$, df = 25, $p = 0.03$).

NART Verbal IQ scores for five controls and BDI scores for two controls were missing. The patients with schizophrenia were rated on the Scale for Assessment of Positive Symptoms (Andreasen, 1984) and the Scale for Assessment of Negative Signs (Andreasen, 1983) and as a group had higher ratings of negative signs than positive symptoms ($t = 5.23$, df = 12, $p < 0.001$).
Table 6.2. Details of subject groups. All values given are means, standard deviations in brackets. SAPS = The standardised assessment for positive symptoms (Andreasen, 1984). SANS = The standardised assessment for negative symptoms (Andreasen, 1983)

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Patients with Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.5 (8.2)</td>
<td>41.3 (6.5)</td>
</tr>
<tr>
<td>Beck Depression Inventory (0 – 63)</td>
<td>6.4 (6.5)</td>
<td>15.0 (8.0)</td>
</tr>
<tr>
<td>SAPS (0 – 175)</td>
<td></td>
<td>6.1 (8.0)</td>
</tr>
<tr>
<td>SANS (0 – 120)</td>
<td></td>
<td>18.9 (12.0)</td>
</tr>
<tr>
<td>Dose anticholinergic (Disipal equivalent)</td>
<td>37.5 (71.1)</td>
<td>(range 0 – 200 mg)</td>
</tr>
<tr>
<td>Dose neuroleptic (chlorpromazine equivalent)</td>
<td>377.1 (305.9)</td>
<td>(range 0 – 825 mg)</td>
</tr>
</tbody>
</table>
Figure 6.1 The four priming conditions. The probe target could either share (C+) or not share (C-) colour with the prime distractor, and it could either share (L+) or not share (L-) location with the prime distractor. The lower case letters adjacent to the boxes specify the colours of the uppercase target and distraction letters (X) within the boxes. The lower case letter in the central box indicates the colour of the colour selection cue (b = blue, g = green, p = purple, y = yellow).
6.2.2 Task

The task was the same as that in experiment 3 of Tipper et al. (1995). Figure 6.1 presents the prime and probe conditions. The subject initiated each trial by pressing the start key that was located under the index finger on the joystick. After pressing the start key four empty boxes appeared which indicated the possible stimulus locations, above, below, to the left and right of fixation. After a delay of 1000 ms the prime display appeared, which were 2 Xs of different colours that appeared in two randomly chosen boxes, and a small coloured square presented at fixation simultaneously with the 2 Xs (in Tipper et al.'s (1995) experiment 3 the coloured square appeared 57 ms after the onset of Xs and remained on the screen for 29 ms). One X was the same colour as the small central square. Subjects were instructed to move the joystick in the direction of the target X, the colour of which matched the central coloured square which acted as the colour selection cue. Both speed and accuracy were emphasised. The prime remained on the screen until the subject responded. Auditory feedback was given in the form of an error tone for an incorrect response and a 50 ms click for a correct response.

The response stimulus interval (RSI) was 500 ms and only the four boxes were visible during this interval. The probe colour selection cue appeared after the 500 ms RSI and at the same time two coloured Xs were presented. As for the prime, the subjects were required to move the joystick in the direction of the X that matched the central coloured square which acted as the colour selection cue. Both speed and accuracy were emphasised. As for the prime, the display remained on the screen until the response was made, and auditory feedback was provided on each trial. After the auditory feedback following the response to the probe a written prompt appeared on the screen instructing the participant to press the start key to continue.
6.2.3 Design

The study had a mixed between-groups and within-subjects design. The between groups factor was Groups (schizophrenia vs normals). There were 2 repeated measures within subject variables, Location and Colour. There were two levels of Location: L+ and L-. In L+ condition, the probe target appeared in the same location as the prime distractor; and in the L- condition, the probe target appeared in a box that differed from the location of the prime distractor and was vacant during the prime. In all conditions, the probe distractor appeared in a previously vacant box. The two levels of Colour were C+ and C-. In C+ condition, the probe target was the same colour as the prime distractor; in C- condition, the probe target was in a different colour than the prime target or distractor. In all conditions, the probe distractor appeared in a colour that was not used for the prime. Therefore there were four conditions: C- L- (colour mismatch, different location - control), C- L+ (colour mismatch same location - ignored repetition), C+ L- (colour match different location - control), C+ L+ (colour match same location - ignored repetition). There were 4 possible locations; above, below, to the left and right of the central square and there were also 4 possible colours: blue, green, yellow, and purple, selected to be easily discriminable.

Each condition started with a practice block (Block 0) followed by a test block (Block 1). The number of trials for the two types of block in each of the 4 conditions is listed below.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Block 0</th>
<th>Block 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-L-</td>
<td>12</td>
<td>96</td>
</tr>
<tr>
<td>C-L+</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>C+L-</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>C+L+</td>
<td>3</td>
<td>24</td>
</tr>
</tbody>
</table>
These proportions were used to ensure that subjects could not use properties of the prime distractor to predict the colour or location of the probe target. Stimulus presentation and RTs were measured to the nearest ms. Millisecond timing of displays and responses was achieved using the TIMEX function (Bovens and Brysbaert, 1990). The data of importance were the median RTs for correct responses and error percentages. Prime and probe RTs were used only if the responses to both prime and probe were correct. Responses greater than 3000 ms were counted as errors. The four conditions were randomised in terms of order of presentation. All 243 trials were presented in one session, with a 30 second break after every 50 trials. The first 27 trials were practice and not included in the analysis. The entire session lasted approximately 30 minutes.

6.3 Results

6.3.1 Prime Displays
A one way Analysis of Variance (ANOVA) was used to examine the RT for the prime condition. RTs for the patients with schizophrenia were significantly slower than those for the normals \[F(1, 27) = 21.92, p < 0.01\]. A one way ANOVA was carried out on the percentage of errors in the prime condition. The patients with schizophrenia and the normals did not differ in terms of percent of errors made \[F(1, 27) = 0.23, p > 0.05\].

6.3.2 Probe Display
A 3 way ANOVA was carried out. The between subjects factor was Group (schizophrenia vs normals) and the within subject variables were Colour (C+ vs C- ) [colour match or colour mismatch] and Location (L+ vs L-) [ignored repetition or control]. The mean median RTs for each condition in each group are shown in Figure 6.2.
The main effect of Colour was not significant \[F(1, 27) = 0.19, p > 0.05\]. The main effect of Group was significant \[F(1, 27) = 19.22, p < 0.01\] due to slower RTs for the patients (725 ms, SD = 108) than for the normal controls (566 ms, SD = 87). The main effect of Location \[F(1, 27) = 31.12, p < 0.01\] was also significant as RTs were slower for the ignored repetition conditions (L+) (641 ms, SD = 121) than for the control conditions (L-) (623 ms, SD = 127). There was no significant Colour x Location interaction, nor did Group show a significant interaction with either of the other two variables (p > 0.05). The three way Group x Colour x Location interaction was also nonsignificant (p > 0.05).

Given my interest in negative priming effects (control conditions compared to ignored repetition conditions) a series of post hoc tests were carried out. In normals, the comparison of C+ L- and C+ L+ was significant (t = 3.9, d.f. = 16, p < 0.01). T-tests revealed that the normals also had significantly slower RTs in the C-L+ than in the C-L- condition (t = 4.7, d.f. = 16, p < 0.001). Thus the normal controls exhibited significant spatial negative priming in both the colour match and colour mismatch conditions.

However, these same comparisons for the patients with schizophrenia were not significant. The RTs for the patients with schizophrenia did not differ significantly between the C+L+ condition and the C+L- condition (p > 0.05) (colour match) or between the C-L+ condition and the C-L- condition (p > 0.05) (colour mismatch). Therefore the patients with schizophrenia failed to show significant spatial negative priming in either the colour match or the colour mismatch condition.
Figure 6.2 The mean of median reaction times (RTs) to the probes for the patients with schizophrenia and normal controls in each of the four conditions C-L- control, colour mismatch; C-L+ ignored repetition, colour mismatch; C+L- control, colour match; C+L+ ignored repetition, colour match. Spatial negative priming is indicated by slower RTs for ignored repetition (L+, white bars) than control (L-, black bars) conditions for the normal controls. *Significance p < 0.05.
6.3.3 Probe Error Data
The mean percentage of errors for each group in each condition are presented in Table 6.3. A 3 way repeated measures ANOVA was carried out on the error percentages. The between subjects factor was Group (patients with schizophrenia vs normals) and the within subject variables were Colour \((C+ \text{ vs } C-)\) and Location \((L+ \text{ vs } L-)\). There were no significant main effects of Group, Colour, or Location \((p > 0.05)\) and there were no significant interactions \((p > 0.05)\).

Table 6.3. Mean percentage of errors (and standard deviations) for each group in each condition - \(C+L+:\) the probe target was the same colour and appeared in the same location as the prime distractor; \(C+L-:\) the probe target was the same colour but appeared in a different location to the prime distractor; \(C-L+:\) the probe target was a different colour but in the same location as the prime distractor; \(C-L-:\) the probe target was a different colour and was in a different location than the prime distractor.

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Patients with schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-L-</td>
<td>1.40 (1.47)</td>
<td>2.33 (2.51)</td>
</tr>
<tr>
<td>C-L+</td>
<td>1.11 (1.31)</td>
<td>2.79 (2.86)</td>
</tr>
<tr>
<td>C+L-</td>
<td>1.98 (1.74)</td>
<td>1.58 (2.03)</td>
</tr>
<tr>
<td>C+L+</td>
<td>1.47 (2.91)</td>
<td>2.78 (4.10)</td>
</tr>
</tbody>
</table>

6.3.4 Correlational Analysis.
To determine the extent of the spatial negative priming effect the RTs for the ignored repetition conditions were subtracted from the RTs for their respective control conditions: \([C-L-] - (C-L+)\] for the colour mismatch condition, and \([C+L-] - (C+L+)\] for the colour match condition. Pearson’s correlations were used to examine the relationship between the individual symptoms of schizophrenia as rated on the SANS/SAPS, depression as rated on the Beck Depression Inventory, errors scores and the spatial negative priming effects. The results are presented in Table 6.4. The p

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values were adjusted for the number of correlations (77) by carrying out a Bonferroni correction. After this adjustment there was one significant correlation. There was a significant positive correlation between rating of bizarre behaviour and the magnitude of the spatial negative priming effect for the colour mismatch condition (r = 0.86, p < 0.001). This means that a higher rating of bizarre behaviour was associated with a reduced (i.e., impaired) negative priming effect for the Colour Mismatch condition.

There is a possibility that factors such as levels of neuroleptic medication, depression, or cognitive deficits, which have been shown to differ among patients with schizophrenia, could confound the findings of correlational analyses. Therefore, Pearson’s Partial Correlations were run controlling for dose of neuroleptic, BDI score, and NART Verbal IQ score. These results are presented in Table 6.5. After the Bonferroni adjustment for the number of correlations (70) there were no significant correlations.
Table 6.4 Pearson's correlations between measures of Spatial Negative Priming effect, errors and the individual symptom ratings of the Schedule for the Assessment of Positive Symptoms (SAPS) and the Schedule for the Assessment of Negative signs (SANS). The r and p values are given. Only coefficients with p < 0.05 are presented.

<table>
<thead>
<tr>
<th></th>
<th>SAPS SANS</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Thought Disorder</td>
<td>Bizarre Behaviour</td>
<td></td>
</tr>
<tr>
<td>Spatial Negative Priming Effect</td>
<td>r = 0.86 p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colour Mismatch</td>
<td>r = 0.7 p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control condition (C-L-) Errors</td>
<td>r = 0.69 p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colour match condition (C+L-) Errors</td>
<td>r = 0.7 p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Errors</td>
<td></td>
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</table>

Table 6.5 Pearson's Partial correlations between measures of Spatial Negative Priming effect, errors and the individual symptom ratings of the Schedule for the Assessment of Positive Symptoms (SAPS) and the Schedule for the Assessment of Negative signs (SANS) controlling for medication, level of depression and Mini Mental score. The r and p values are given. Only coefficients with p < 0.05 are presented.

<table>
<thead>
<tr>
<th></th>
<th>SAPS/SANS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thought Disorder</td>
<td>Bizarre Behaviour</td>
<td></td>
</tr>
<tr>
<td>Spatial Negative Priming Effect</td>
<td>r = 0.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colour Mismatch</td>
<td>d.f. = 5 p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial Negative Priming Effect</td>
<td>r = 0.76</td>
<td>d.f. = 5</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Colour Match</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colour Match condition (C+L-) Errors</td>
<td>r = 0.8</td>
<td>d.f. = 5</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Errors</td>
<td></td>
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</tbody>
</table>
6.4 Discussion

In summary, the significant main effect of location signified occurrence of significant spatial negative priming. The main effect of colour was not significant indicating that colour match or mismatch did not affect RTs. The groups differed significantly reflecting slower RTs for the patients with schizophrenia than for the normal controls. There were no significant group interactions but post-hoc comparisons revealed that the normals showed significant spatial negative priming effects both in the colour match and in the colour mismatch conditions, while the patients with schizophrenia failed to exhibit significant levels of negative priming effects in either condition.

It has been proposed that the increased RT previously attributed to spatial negative priming effects may be due to perceptual mismatch since the prime distractor differed from the probe target in terms of either colour, identity, or size (Park and Kanwisher, 1994). The current results add support to the findings of Milliken et al. (1994) and Tipper et al. (1995) that in normal subjects spatial negative priming effects are present even when other stimulus features such as colour, identity and size are held constant between the prime distractor and the probe target. In the present study there was no significant difference in the degree of spatial negative priming effects between the colour match and the colour mismatch condition.

Recently, Tipper (1998) has noted that the accounts of negative priming in terms of inhibition of the internal representation of a distractor in the process of selective attention or detection of perceptual mismatch in the process of episodic retrieval which have respectively been described as forward acting and backward acting processes are not necessarily antagonistic or mutually exclusive. Instead, Tipper suggests that as both encoding and retrieval processes are implicated in the negative priming phenomenon;
the inhibition account which emphasises the encoding process acting on the prime display and the episodic account which focuses on the properties of the probe that enable retrieval of the prime encoding episode are both relevant to a fuller understanding of negative priming effects. In this respect, both accounts are relevant to appreciation of reduced negative priming in schizophrenia as these patients also show deficits in episodic encoding and retrieval (Brebion et al., 1997; Andreasen, 1997) as well as inhibitory processes (see Introduction).

Evidence implicates dopamine as a neurotransmitter with a role in mediating negative priming. However the precise direction and nature of this role is unclear. David (1995) has noted that in the more acute phase, when positive symptoms predominate, reduced negative priming in schizophrenia has been attributed to a hyper-dopaminergic state. However, several lines of evidence oppose such a view. First, there is evidence from normal subjects showing that neuroleptics, that is dopamine antagonists, increase negative priming (Beech, et al., 1990). Second, reduced negative priming has been reported in patients with schizophrenia who were (Beech et al, 1989; Laplante et al, 1992) or were not (Salo et al, 1996) tested while taking neuroleptic medication. For example, Salo et al. (1996) tested 12 patients with schizophrenia withdrawn from neuroleptic medication and found no evidence of negative priming. In contrast, David (1995) found that in a small group of neuroleptic free patients with schizophrenia or affective disorder there was some suggestion that negative priming was present. Third, patients with Parkinson's disease, a hypo-dopaminergic disorder, fail to show negative priming (Downes et al., 1991). In reviewing the effects of neuroleptics on cognitive function, Spohn & Strauss (1989) concluded that neuroleptics tend to normalize the performance of patients with schizophrenia and reduce distractibility on attentional tasks. This is clearly not the case for negative priming effects. In the present study, all
patients were on neuroleptic medication and none showed any substantial degree of negative priming as observed in the normal controls. Also, the dose of neuroleptics did not show any significant associations with any of the measures of negative priming. Therefore, available information about the contribution of dopamine overstimulation or understimulation to negative priming is inconsistent. Future studies need to evaluate this question more systematically by examining negative priming in early newly diagnosed patients prior to the introduction of neuroleptic medication, chronic treatment with which may in itself alter dopaminergic transmission.

Because of the post hoc nature of the group differences, it could be argued that the present results constitute relatively weak demonstration of reduced negative priming in patients with schizophrenia. Future studies should include a larger number of participants and patients with higher ratings of symptoms. Reduced negative priming has been demonstrated for patients with schizophrenia and predominance of positive or negative symptoms, with some studies suggesting that the abnormality of negative priming is greater in those with relatively higher ratings of negative symptoms (Laplante et al, 1992), while others report reduced negative priming in patients with positive symptoms (Park et al, 1996; Williams, 1996). The latter study reported reduced negative priming in subgroups of patients with reality distortion and disorganisation. Park et al. (1996) found reduced negative priming in acute but not chronic patients with schizophrenia. In the present study, there were not enough patients with predominance of positive symptoms vs negative signs to compare negative priming across the subgroups. However, the correlational analysis suggests that higher ratings of bizarre behaviour were associated with less negative priming in the colour mismatch condition. This finding suggests weakened inhibition may contribute to positive symptoms in schizophrenia.
Lavie and colleagues (Lavie & Tsal, 1994; Lavie & Fox 1998) have suggested that high perceptual load in processing of relevant information is a necessary condition for early selection to occur. In normals, evidence has been provided to show that with higher perceptual load, distractor interference is reduced. In relation to negative priming, these authors have shown that manipulating the perceptual load of relevant processing by increasing the set size of the target reduced the amount of negative priming associated with processing of a distractor stimulus (Lavie & Fox 1998). Reduced negative priming in schizophrenia can be incorporated into this view of the relevance of perceptual load to negative priming. It can be suggested that because of capacity limitations (Granholm et al., 1996), perceptual load is higher in schizophrenia than normals across all tasks, so that less or no spare capacity is available to allocate to inhibition of irrelevant/distractor stimuli.

It is possible that in negative priming paradigms selective inhibition of the distractor does in fact occur in schizophrenia but it decays more rapidly compared to normal subjects, such that at the time of the probe trial it produces a less detrimental effect on the subsequent act of selection. As an alternative to this ‘rapid dissipation of inhibition’, it is possible that the ‘strength’ of the initial inhibition is somewhat weaker so that it does not build up rapidly or sufficiently enough to carry over into the subsequent act of selection. In future studies, it should be possible to differentiate between these two alternative explanations of reduced negative priming in schizophrenia: rapidly decaying inhibition vs weakened and delayed build up of inhibition. The interval between trial n and n-1 is important in negative priming tasks and Laplante et al. (1992) have shown that the interval between prime and probe trials affects the degree of negative priming observed in patients with predominance of
positive or negative symptoms of schizophrenia. In future studies, supplementing
behavioural investigation of the negative priming effect with recording of event-related
cortical potentials which have high temporal resolution and provide ms by ms data will
be valuable in providing information about the time course of operation of inhibitory
processes between the prime distractor and probe target.

In summary, in normal subjects negative priming was found even when there was no
perceptual mismatch between the ignored prime distractor and the target probe, adding
support to the findings of Milliken et al. (1994) and Tipper et al. (1995). Post hoc
analysis showed reduced negative priming in patients with schizophrenia in conditions
with or without perceptual mismatch. This is the first clear and unequivocal
demonstration of reduced inhibition in schizophrenia based on reduced negative priming
effects.
CHAPTER 7

General Discussion

The results of each study were discussed at length in previous sections. The aim of this chapter is to interrelate the results of the 6 studies in terms of the hypothesis under investigation in order to arrive at some general conclusions.

7.1 Willed Preparation and initiation of action in schizophrenia

Shakow (1962) noted that the disturbance in schizophrenia 'begins to appear at a level of response where voluntary behaviour is involved' pointing out that patients with schizophrenia perform more successfully in conditions controlled by an experimenter while controls do better under conditions of autonomy. Frith (1992) has proposed two routes to action, one which is stimulus driven and the other which is internally driven. In the stimulus driven route, perception of a stimulus triggers an action which leads to the production of a response. In the internally driven, or willed action route, goals and plans lead to the production of intentions, which, in turn, lead to initiation of appropriate actions and the suppression of inappropriate actions resulting in an appropriate response. Frith (1992) has also proposed that the signs and symptoms of schizophrenia arise from a dysfunction of the willed action route, but the stimulus driven route remains intact. In patients with negative signs this impairment exhibits itself in poverty of willed intentions, thus limited action. In patients with positive symptoms this impairment exhibits itself as an inability to inhibit inappropriate stimulus driven action and is manifested as context inappropriate behaviour such as errors of commission. Patients with schizophrenia should have an impaired ability to generate movement, but responses to external stimuli (even if inappropriate) should be intact.
The aim of this thesis was to test these hypotheses and add to the evidence that patients with schizophrenia do show impairments in willed action while stimulus driven actions remain intact.

In Study 1 the patients with schizophrenia had significantly slower RTs and MTs than normals across all RT tasks. In the patients with schizophrenia the fully cued CRTs were unexpectedly equivalent to SRT for the 200 ms interval and expectedly for the 1600 ms S1-S2 interval, but not the 3200 or 800 ms intervals. For the normals fully cued CRTs and SRTs were equivalent for S1-S2 intervals of 800 ms or longer. In the fully cued CRT condition the volitional demands of preprogramming involve preparing a different response for each trial and patients showed unusual and inconsistent interval effects particularly longer RTs for an 800 ms S1-S2 interval than following a 200 ms S1-S2 interval, unlike the normals. These results suggest an instability of attentional set, or an intrusion of the automatic stimulus driven response into willed conscious control in the patients with schizophrenia.

In Study 2 the patients with schizophrenia placed fewer pegs and had reduced tapping speed in unimanual and bimanual conditions. Under dual task conditions, the performance of the patients with schizophrenia in peg placement actually improved relative to the unimanual pegboard task, whereas tapping performance deteriorated compared to the unimanual tapping, a decrement that was significantly greater for the patients. Thus the improvement in the visually guided pegboard task was at the expense of the repetitive tapping task.

In study 3 the patients with schizophrenia and high ratings of negative signs had reduced amplitude of MRPs for the late and peak component and reduced slope of the
early and late MRPs prior to self-initiated movements. These differences were not found prior to externally-triggered movements. The patients with schizophrenia with higher ratings of positive symptoms did not differ significantly from the normal controls in terms of amplitude or slope of MRPs prior to self-initiated or externally-triggered movements.

The strongest finding supporting the hypothesis was the results of Study 3. The reduced MRPs prior to self initiated movements seen in the negative patients suggests that the deficits in willed action in these patients may be mediated by dysfunction of the fronto-striatal circuits. Using similar types of movement as in Study 3, in an investigation combining MRPs and measurements of regional cerebral blood flow (rCBF) with PET, Jahanshahi et al. (1995) found that patients with Parkinson’s disease tested off dopaminergic medication had a lower amplitude of the early and peak but not late BP prior to self-initiated movements than age-matched normals, the performance of which relative to a rest condition was associated with underactivation of the putamen, SMA, anterior cingulate, lateral premotor cortex and dorsolateral prefrontal cortex in these patients relative to normals. A similar study in patients with schizophrenia may provide similar interesting functional anatomical results.

The results of Study 1 and Study 2 provide further supporting evidence that movements requiring volitional control are inferior to the stimulus driven movements in patients with schizophrenia. The unusual interval effects for the patients in the fully cued CRT condition suggest that the willed conscious processes of movement initiation may be interfering with RTs following a fully-cued 800ms S1-S2 interval (which allows time for movement preparation in normals), resulting in slower RTs than those following a 200 ms S1-S2 interval (which does not allow time for preparation in normals and is
therefore purely stimulus driven). In the tapping and pegboard bimanual task the patients appear to improve peg placement by using tapping as an external cue. Taken together, these results provide some evidence that willed action is impaired in schizophrenia compared to stimulus driven action.

In Study 1, however, the patients with schizophrenia were able to improve RTs in the SRT condition, compared to the unwarned and uncued CRT condition. In the uncued and unwarned CRT no preprogramming is possible and the correct response is selected, prepared and initiated only after presentation of the imperative stimulus, and is therefore a purely stimulus driven task. Faster RTs in the SRT than the CRT condition indicate that the patients were able to use optional and volitional preprogramming in the SRT condition to preprogramme the response prior to presentation of the stimulus. This result was contrary to prediction and may be due to the sample of the patients used. For example, the evidence from the results of Study 3 suggest that impairment in the initiation of willed actions is more prevalent in patients with higher ratings of negative signs. It was not feasible to divide the patients in Study 1 into a ‘positive’ group and a ‘negative’ group, due to the relatively small sample size of 10 and low symptom rating scores. Future studies of SRT-CRT comparisons testing patients with higher symptom ratings and using larger sample sizes may reveal more about the symptom-based differences between patients’ ability to preprogramme responses and to use optional and volitional preprogramming to improve RTs in an SRT condition.

Another possible explanation is that patients with schizophrenia have little or no impairment preprogramming movement in SRT and fully cued CRT conditions with a movement parameter precue. There have been many examples of generalised slowness in patients with schizophrenia (Vinogradov et al., 1998; Wigal et al., 1997; Elkins and
Cromwell, 1994; Nestor et al., 1992; Mannuzza et al., 1984) as found in study 1. In a review of the literature on information processing in schizophrenia, Hemsley (1976) concluded that CRT tasks involving low stimulus-response compatibility are more sensitive to deficits in schizophrenia (Venables, 1958; Slade 1971). Perhaps in Study 1 the high compatibility between the stimulus and response enabled the patients with schizophrenia to preprogramme the response. Repeating this study on a large number of patients will help to determine if indeed the patients with schizophrenia have no difficulty preprogramming response in SRT and fully cued CRT conditions. It would also be beneficial to repeat this paradigm and include a condition with reduced stimulus-response compatibility to determine if the patients are able to utilise highly compatible movement parameter precue information similar to controls but show a greater decrement with incompatible movement parameter precue information compared to controls.

The interesting anomaly of the greatly increased RT for the fully cued CRT conditions with 800 ms ISI needs to be investigated further. A study comparing uncued and fully cued CRT conditions with ISIs of 0, 200, 400, 600, 800, 1000, 1200, 1400 and 1600 ms may reveal an interesting phenomenon about the ability of patients with schizophrenia to use advance information over varying preparatory periods to preprogramme movement. In Study 1 the patients with schizophrenia were able to use the advance movement parameter information provided to preprogramme movement if given 1600 ms after the warning signal to prepare the movement. The patients were significantly more impaired, however if they had 800 ms to prepare movement then if they had 200 ms to prepare. Investigating smaller increments in ISI could pinpoint how much time in an ISI is useful and how much time is detrimental to movement preparation in schizophrenia. Alternatively, Study 1 could be replicated using ERPs which would
provide temporal data in the ms range to clarify the time course of motor preparation in advance of the imperative stimulus for the varying ISIs, that may help clarify the abnormal interval effects for the patients.

In Study 2 the group of patients with schizophrenia had significantly higher levels of depression than the group of controls. An interesting finding of Study 2 is that after controlling for depression and mini mental scores there were no significant decrements in tapping or peg placement for the patients with schizophrenia relative to controls. This suggests that the impairments in performance seen in the patients, were more related to the high levels of depression than the diagnosis of schizophrenia. The existing literature on tapping performance in depression and schizophrenia is contradictory. Depressed patients are reported to have reduced tapping in dual task paradigms that include tapping in conjunction with a cognitive task (Hillis 1998, Volf et al., 1993) and one study found impaired pegboard performance in depressed compared to non depressed HIV positive patients (Hinkin et al., 1992). Patients with schizophrenia are reported to have reduced tapping compared to depressed patients (Harris et al., 1981) but no difference was found between patients with schizophrenia and patients with bipolar disorder on pegboard performance (Hoff et al., 1990). It is therefore possible that the impairments seen in Study 2 are in part due to depression. To ascertain this, Study 2 could be replicated by comparing patients with schizophrenia, patients with major depression, and a group of normal controls or patients with high vs low depression to tease out if impaired dual task performance is associated with schizophrenia, depression, or both.

A second interesting, and unexpected finding of Study 2 is that higher ratings of the positive symptom of incoherence were associated with reduced peg placement in the
dual task condition. While reduced peg placement has been reported in patients with schizophrenia (Flashman et al., 1996; Classen and Laux, 1991) and patients with Parkinson’s disease (Limousin et al., 1999; Brown and Jahanshahi, 1998; Brown et al., 1993) there have been no reports of impaired peg placement associated specifically with any of the positive symptoms of schizophrenia, either psychotic or disorganised. It has been shown that decreased motor activity is associated with negative signs and increased motor activity is associated with the disorganised positive symptoms (Johnstone and Frith, 1996). This finding requires replication with a larger number of patients with schizophrenia, one group with high ratings of disorganised positive symptoms (thought disorder, bizarre behaviour, incoherence) one group with high ratings of psychotic positive symptoms (hallucinations and delusions) and one group with high ratings of negative signs (alogia, avolition, flattened affect).

7.2 Willed Suppression in Schizophrenia

Studies 1, 2 and 3 provided evidence that patients with schizophrenia have impaired performance on tasks requiring self-initiated movements, while their stimulus driven movements are intact. Studies 4, 5 and 6 were designed to determine if the patients with schizophrenia are impaired in tasks requiring the use of willed suppression to inhibit stimulus driven behaviour when it is more or less automatic, yet inappropriate.

In Studies 4 and 5 the patients with ‘high symptoms’ had significantly slower RTs than the controls in SRT conditions, however, group differences in RTs of the CRT conditions only approached significance. The patients with ‘high symptoms’ in Studies 4 and 5 were unable to use the volitional and optional preprogramming in the SRT and were therefore significantly slower than the controls. In the stimulus driven CRT conditions of Studies 4 and 5 the patients with ‘high symptoms’ were only marginally
slower than the controls. If these results are compared to the SRT-CRT comparison of Study 1, we see that higher symptom ratings may be crucial to volitional impairments. As the patients were high on both positive symptoms and negative signs, however, it is not clear whether it is one set of symptoms or both which has a greater association with the impairment.

Impaired performance on the no-go tasks of Studies 4 and 5 were associated with impaired performance on the cognitive tasks requiring response suppression. These correlations suggest that the go no-go tasks and the cognitive tasks may both be tapping some common ability to inhibit or suppress inappropriate responses for selection or release of the appropriate response.

Patients with frontal lobe damage are impaired on no-go tasks (Drewe, 1975; Leimkuhler and Mesulam, 1985; Godefroy et al., 1996). As an increased number of errors in the no-go tasks correlated with impaired performance on the tasks of ‘frontal’ function, the results suggest that the go no-go paradigm is a valid tool for investigating frontal impairment in patients with schizophrenia. It is possible that because of the low symptomatic state the sample of patients were not representative of the population of patients with schizophrenia, as there was little impairment seen in the frontal lobe tasks, in which patients with schizophrenia, traditionally, perform poorly.

The surprising finding of Study 4, that RT was fastest in CRT3 for both patients and controls, could have been avoided by utilising a pilot study in a group of normal controls. The paradigm could then have been altered to more closely resemble the original study by Cooper et al. (1994), who used a tone as one of the experimentally manipulated stimulus dimensions. However, when designing the study, we decided
against the use of a tone because of the 'modality shift' effect in schizophrenia. This refers to the finding that a shift from a visual stimulus to an auditory stimulus lengthens RT in schizophrenia to a greater degree than in normal controls (Ferstl et al., 1994, Mannuzza, 1980).

Another area of interest regarding studies 4 and 5 is the effect of the interstimulus interval on RT in schizophrenia which was shown to be important in distinguishing patients from normals in Study 1. There was no warning signal in the go no-go RT tasks, but there was a time delay of .5, 1 or 2 seconds between the disappearance of the fixation cue and the appearance of the imperative stimulus. It would be interesting to repeat the study using a fixation-cue- imperative cue interval of 200, 800, and 1600 ms in order to see if a similar 800ms interval anomaly is found in the no-go study as was seen in Study 1. In addition, the no-go study could be repeated with warning signals and the effect of ISIs of 200, 800, and 1600 ms could be investigated.

In Study 6 the controls exhibited spatial negative priming, as defined by slowed RTs that occur when an ignored distractor stimulus in a first trial becomes the target stimulus in the subsequent trial. The patients with schizophrenia did not exhibit spatial negative priming in the condition for which the identity of the prime distractor matched or did not match the colour of the probe target. As this was the first study of negative priming in patients with schizophrenia to control for the possible artifact of perceptual mismatch, the results here signify that reduced spatial negative priming in schizophrenia can unequivocally be attributed to a failure of inhibition. This argument for failed inhibition is based on significant post hoc tests in Study 6, as the main interaction effect of Group and Condition was not significant. However, the lack of strong results may be due to mild symptom ratings in the patient group, but when the reduced spatial negative
priming found in the patients of Study 6 is considered in conjunction with the impaired inhibition of habitual responses on some of the cognitive tasks required willed suppression in Studies 4 and 5 and the increased number of errors of anticipation and commission in Study 4, this suggests that patients with schizophrenia fail to wilfully inhibit stimulus-driven behaviour.

It was interesting that the higher ratings of bizarre behaviour were associated with reduced spatial negative priming in the colour mismatch condition of Study 6. This finding suggests weakened inhibition may contribute to positive symptoms in schizophrenia, especially the disorganized symptoms. Disorganisation has been associated with increased errors of commission on the Continuous Performance Test (Johnstone and Frith, 1996), also indicative of weakened inhibition. Given these findings it is surprising that there was no association between errors of commission in Study 4 and 5 and any of the disorganised positive symptoms. Again, this may be due to the relatively small sample size and low symptomatology. It would be interesting to administer the negative priming, no-go RT tasks, and cognitive tests requiring inhibition to a larger group of patients, with one subset having high rates of negative signs and one subset having high rates of disorganised symptoms and one subset having high rates of psychotic symptoms, to determine if it is possible to differentiate among the performances of the three groups. It would be predicted that patients with high ratings of negative signs would have the slowest RT of the three groups reflecting psychomotor poverty and the patients with high ratings of disorganised symptoms would have the greatest number of errors of commission in the no-go and cognitive inhibition tasks and the greatest reduction in spatial negative priming effect in the negative priming study, reflecting impaired inhibition.
The reduced inhibition in spatial negative priming found in Study 6 resembles the findings of the Kamin blocking effect (Lubow, 1982) and latent inhibition (Lubow et al., 1982). In the spatial negative priming paradigm patients with schizophrenia show less interference from the prime stimulus-response pairing than the controls, similar to the findings of the Kamin blocking effect (Lubow, 1982) and latent inhibition studies (Lubow et al., 1982). Also higher ratings of bizarre behaviour were associated with a greater reduction of the spatial negative priming effect in patients with schizophrenia linking the phenomenon of reduced stimulus-response pairing with positive, disorganised symptoms.

This interesting finding of reduced spatial negative priming in patients with schizophrenia and its link to the disorganised symptom of bizarre behaviour supports the lateralization theory (Gruzelier, 1984), according to which the active syndrome in schizophrenia is associated with poorer spatial than verbal performance (Gruzelier et al., 1988; Gruzelier, 1991). It would be very interesting to repeat the spatial negative priming study and include a test of verbal performance to see if a double dissociation occurs between the patients with negative signs and the patients with disorganised symptoms. Based on the laterality theory (Gruzelier et al., 1988; Gruzelier, 1990) and the findings of Study 6, it would be predicted that the patients with disorganised symptoms would show a greater reduction in spatial negative priming than the patients with negative signs while the patients with negative signs would be more impaired on the verbal task than patients with disorganised symptoms.
7.3 Possible Anatomical Substrates of Cognitive Deficits

It is generally accepted that the frontal lobes are responsible for 'executive function' such as those which involve planning, decision making, error correction, inhibiting habitual responses (e.g. Shallice, 1988) and that patients with schizophrenia are impaired on various tests of executive function (e.g. Goldberg et al., 1989, Liddle et al., 1991). In schizophrenia impaired prefrontal activation during performance of tasks requiring volitional control (Weinberger et al., 1988; Andreasen et al., 1992; Seidman et al., 1994), reduced activation of the SMA (Schroeder et al., 1994) and an association between poverty of action and decreased rCBF in the dorsolateral prefrontal cortex and increased rCBF in the caudate (Liddle et al., 1992) have been reported. Patients with schizophrenia and poverty of speech have shown reduced activation of the left DLPFC (Dolan, et al., 1993). Compared to a word repetition task, a word generation task was associated with increased activity in the left dorsolateral prefrontal cortex and the anterior cingulate cortex and decreased bilateral activity of the superior temporal cortex in normals. Patients with schizophrenia failed to show the reduced activity in the left temporal cortex (Dolan et al., 1995; Frith et al., 1995) suggesting that fronto-temporal connectivity is impaired. Patients with schizophrenia with high error rates on the antisaccade task, a task requiring inhibition of automatic eye movements, showed reduced activation of the anterior cingulate, insula and the left striatum (Crawford et al., 1996). Jahanshahi and Frith (1998) have provided strong support for the involvement of the fronto-striatal circuits in willed action. Therefore, it is possible that the deficits in willed initiation and suppression of action observed in some studies in the present series would be mediated by the fronto-striatal circuits.
7.4 Symptom Severity and Neuropsychological Results

The effects of the clinical signs and symptoms of schizophrenia on cognitive function have been investigated with varying results. In some studies it has been found that patients rating high on positive symptoms were impaired on tasks requiring them to monitor their own self generated actions (Frith and Done, 1989; Mlakar et al., 1994) and that the positive symptoms of thought disorder were related to neuropsychological impairment but negative signs were not (Dickerson et al., 1991). Other studies have found that greater neuropsychological impairments correlated with ratings of negative signs (Braff et al., 1991; Kay et al., 1986; Merriam et al., 1990), while still others show no relation between symptoms and neuropsychological performance on tests such as the WCST (Green et al., 1992) the Stroop task or the California Verbal Learning Test (Hoff et al., 1992). Green (1996) found that instead of symptom severity, tests such as WCST and CPT were associated with functional outcome in terms of community living and skill acquisition (Mortimer 1997).

7.5 The Limitations of the Present Studies

The results of the Studies 1-6 provide some evidence that patients with schizophrenia are impaired on tasks requiring willed action while stimulus driven action remains intact, and the impaired performance in patients with schizophrenia may reflect frontal lobe impairment and may be linked with symptom severity. These findings, however, were not as consistent across the different tasks in the six studies as expected. This suggests that the tasks used in the six studies differed in their sensitivity to unravel deficits in willed initiation or suppression of action in schizophrenia. A second consideration in light of well recognised high individual variability in schizophrenia
samples is the relatively small sample size. Frith (1992) has noted that many psychological studies of schizophrenia suffer from the fact that large groups of patients are often used who have symptoms and signs which vary greatly from subject to subject. If certain signs and symptoms are related to specific cognitive deficits, then an averaged score from a particular test based on a large heterogeneous group may provide misleading results. Evidence for this has been provided by Liddle and Morris (1991) who have shown that patients whose signs and symptoms cluster into different categories perform differently on neuropsychological tests. Attempts were made in the current studies to recruit patients either with high levels of negative signs or high levels of positive symptoms. There were difficulties in obtaining large numbers of patients fitting these criteria mainly because, those individuals suffering from high levels of avolition are not willing to participate in research studies and those individuals suffering from high levels of psychotic symptoms are hospitalised and therefore not testable. The patients with schizophrenia who volunteered for these studies were mostly outpatients, many of whom had responsibilities such as part-time jobs or families. Consequently the patients used had relatively low levels of symptom ratings. This may have been an important factor contributing to the lack of more clear-cut deficits in Studies 4, 5 and 6.

Another potential shortcoming of the current series of studies, particularly evident in Study 2, was the use of normal controls as the only comparison group. Using another patient population such as depressed patients would allow for the possible confounding effects of hospitalisation and long-term illness to be accounted for.

It has been suggested that results from neurocognitive or psychophysiological tests are more informative about the processes seen in the short-term state variables than the long-term trait variables of schizophrenia (Johnstone and Frith, 1996). The results of
Studies 1 - 6 offer some support of this. The patients with high ratings of negative signs in Study 3 had a greater reduction in slope and amplitude of the MRP prior to self-initiated movements than the patients with high ratings of positive symptoms. It is possible, that retesting any of the ‘positive’ patients when their positive symptoms have decreased and their negative signs have increased will result in reduced slope and amplitude of the MRP prior to self-initiated movements compared to their current results. The patients used in Studies 1, 2, 4, 5, and 6 had relatively low ratings of symptoms and were only mildly impaired on the tasks. Three conclusions could be drawn; the first is that patients with schizophrenia are not impaired in willed initiation or inhibition of action. The second possible conclusion is that the tasks used are not tapping the impairments, if there are any, in the willed initiation and inhibition of action in patients with schizophrenia. The third possible conclusion is that the samples used were not representative of the population of patients with schizophrenia. The patients with schizophrenia used in these studies, were only mildly impaired. The second conclusion is unlikely as some of the same tests (SRTs and CRTs, pegboard and tapping, movement related potentials) have been used to assess patients with Parkinson’s disease and shown to be sensitive to impairments of willed action in this disorder in previous studies (Jahanshahi et al., 1992; Brown et al., 1993; Brown and Jahanshahi, 1998; Jahanshahi et al., 1995). In relation to the first and the third conclusion, the only way to confirm or refute the presence of impaired performance of the initiation and inhibition of actions in schizophrenia is to repeat the studies with very large samples of patients to allow for the heterogeneity in performance found in these patients. Such large sample sizes were unattainable in the current situation. In addition, functional imaging techniques such as PET or fMRI can be used to further investigate willed action in schizophrenia. All of the studies conducted in this thesis, with a few methodological adjustments, could be feasible as imaging studies. Observing patterns
of brain activation associated with task performance may offer more insight into the
differences between patients with schizophrenia and controls on performance of willed
action and the differences between those with high negative or positive symptoms
within the patient group.

7.6 Conclusion
This thesis has provided some clear support for the hypothesis that patients with
schizophrenia have impairments in willed action. First, in patients with negative signs
this was seen as reduced MRPs prior to self initiated movement. Second, in a dual task
condition requiring volitional controls of performance, patients used external pacing
from the tapping task to improve performance in peg placement. Third, the patients
exhibited inconsistencies of ‘set’ in fully-cued CRT tasks with varying S1-S2 intervals.
Impairments in willed action can also be expressed as an inability to suppress attention
to external stimuli. Some albeit less strong evidence of such an impairment in patients
with schizophrenia was observed by (i) the increased errors of commission in the go no-
go task for patients with ‘high symptoms’ as well as (ii) the finding that unlike normals
whose RT was affected by the number of non-target no-go stimuli, the patients with
‘low symptoms’ were most affected by the degree of dimensional overlap between the
go and no-go stimuli and finally (iii) reduced spatial negative priming not attributable to
perceptual mismatch and indicative of failure of inhibition.

Future studies with other relevant experimental tasks for assessing willed initiation and
suppression of action on larger sample sizes, patients with higher severity of symptom
ratings, and using groups of patients who are homogenous in terms of symptoms could
be informative. Functional imaging studies could be also informative. In effect, we
(Jahanshahi, Dirnberger, Fuller, and Frith, 1999) are conducting a study examining the
functional anatomy of random number generation, a willed action task that requires
response selection through suppression of habitual counting, in patients with
schizophrenia. The preliminary results suggest that during RNG the patients do not
show the significant activation of the left dorsolateral prefrontal cortex, the SMA, and
the anterior cingulate, observed in normals. Future imaging studies of go no-go RT
tasks in schizophrenia may shed light over the differences in brain activation in patients
relative to normals.
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List of Publications from this Thesis


Fuller R and Jahanshahi M (1999b) Impairment of willed actions and use of advance information for movement preparation in schizophrenia *Journal of Neurology, Neurosurgery and Psychiatry*, 66, 502-509


Fuller R, Dirnberger G, Frith C, Jahanshahi M (in preparation) Behavioural suppression in a go no-go reaction time task in schizophrenia: The effect of choice complexity and target/distractor similarity on response inhibition
Reprints of Publications
CONCURRENT PERFORMANCE OF MOTOR TASKS AND PROCESSING CAPACITY IN PATIENTS WITH SCHIZOPHRENIA

Rebecca Fuller, Marjan Jahanshahi

Abstract
Any task is carried out more successfully if we allocate undivided attention to it, but as demands on attentional capacity increase—for example, in concurrent or dual task conditions—performance on attended tasks becomes more impaired. Patients with schizophrenia show impaired performance on tasks requiring high levels of attentional capacity. This study examines performance of 11 patients with schizophrenia and 13 normal controls on two motor tasks (placing pegs in a pegboard and repetitive index finger tapping) under unimanual, bimanual, and dual task conditions. The patients with schizophrenia placed fewer pegs and had reduced tapping speed in unimanual and bimanual conditions. However, the decrement in bimanual performance as a percentage of unimanual performance was not significantly different for the patients and controls on either the pegboard or tapping tasks. By contrast, under dual task conditions, the performance of the patients with schizophrenia in peg placement actually improved relative to the unimanual pegboard task, whereas tapping performance deteriorated compared with the unimanual tapping. A decrement that was significantly greater for the patients. Thus the improvement in the visually guided pegboard task was at the expense of the repetitive tapping task. These results are discussed in terms of an impairment of self-initiated movement with general sparing of externally triggered movements in schizophrenia and the role of frontostriatal loops in this process.

Keywords: schizophrenia; dual task; processing resources; finger tapping; Purdue pegboard

Any task is carried out more successfully if we allocate our undivided attention to it. As demands on attentional capacity increase—for example, in concurrent or dual task conditions—performance on attended tasks becomes more impaired. The degree to which a task is impaired, however, depends on the amount of attentional capacity it demands. An automatic task would not interfere with a more demanding task but there would be interference of one very demanding task on another. Schizophrenia is a psychiatric disorder characterised by positive symptoms (for example, hallucinations and delusions) and negative signs (for example, flattening of affect, poverty of speech, and social withdrawal). It has been suggested that as cognitive load increases, patients with schizophrenia show greater task impairment than normal subjects, signifying resource limitations in this disorder. One way to test the effects of increasing cognitive load is to compare performance on dual task with single task conditions. It would be expected that the degree of performance decrement in a dual task compared with a single task condition would be greater in patients with schizophrenia than in controls, due to the patients' limited resources and hence inability to adequately handle the increased cognitive load. There is evidence that under dual task conditions patients with schizophrenia are differentially more impaired than normal subjects and other psychiatric patients. These studies used a simple reaction time task and tests of cognitive skill, such as a visual search task or counting.

Another way to investigate attentional processing capacity in schizophrenia is to assess concurrent performance of motor tasks such as finger tapping and peg placement, which differ in terms of their attentional demands. Peg placement as in the Purdue pegboard task involves sequential movements such as grasping and picking a peg up, followed by its transport and insertion into the holes on the pegboard. Because of its visually driven nature, performance on the pegboard seems to gain prominence over repetitive index finger tapping, which can be performed in a more automatic fashion. As a result, in normal subjects, when performed concurrently, finger tapping interferes relatively less with peg placement, whereas concurrent peg placement affects finger tapping more. The aim of this study was to examine processing resources in schizophrenia by comparing the performance of two motor tasks, tapping and pegboard placement, under unimanual, bimanual, and dual task conditions in patients with schizophrenia and normal controls.
Concurrent motor tasks and processing capacity in schizophrenia

Performance of the two groups on the tapping and Purdue pegboard tasks (mean (SD)) under unimanual, bimanual, and dual task conditions

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenic patients</th>
<th>Normal controls</th>
<th>p Value</th>
<th>(p^*) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegboard unimanual</td>
<td>13.1 (2.3)</td>
<td>16.3 (1.8)</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pegboard bimanual</td>
<td>11.3 (2.8)</td>
<td>14.1 (1.7)</td>
<td>&lt;0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>% Of unimanual pegboard</td>
<td>85.4 (10.1)</td>
<td>87.2 (7.6)</td>
<td>0.53</td>
<td>0.74</td>
</tr>
<tr>
<td>Tapping unimanual</td>
<td>145.5 (40.0)</td>
<td>172.6 (19.1)</td>
<td>0.05</td>
<td>0.19</td>
</tr>
<tr>
<td>Tapping bimanual</td>
<td>132.8 (38.7)</td>
<td>165.2 (26.4)</td>
<td>&lt;0.03</td>
<td>0.26</td>
</tr>
<tr>
<td>% Of unimanual tapping</td>
<td>92.7 (15.0)</td>
<td>94.2 (9.8)</td>
<td>0.77</td>
<td>0.55</td>
</tr>
<tr>
<td>Pegboard with tapping</td>
<td>13.3 (2.5)</td>
<td>15.0 (2.1)</td>
<td>&lt;0.04</td>
<td>0.30</td>
</tr>
<tr>
<td>% Of unimanual pegboard</td>
<td>101.3 (5.2)</td>
<td>92.5 (8.7)</td>
<td>&lt;0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>Tapping with pegboard</td>
<td>100.8 (38.3)</td>
<td>149.6 (22.3)</td>
<td>&lt;0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>Pegboard bimanual</td>
<td>71.2 (25.9)</td>
<td>86.8 (9.8)</td>
<td>0.05</td>
<td>0.26</td>
</tr>
<tr>
<td>% Subjects showing no change</td>
<td>45.5</td>
<td>15.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Subjects showing no change</td>
<td>27.3</td>
<td>7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Subjects showing deterioration</td>
<td>27.3</td>
<td>76.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*Results of one way ANCOVA with MMS and BDI score as covariates.

Method

SUBJECTS
Eleven (two female, nine male) subjects with a clinical diagnosis of schizophrenia according to the DSM III-R criteria were tested. Each was seen as an outpatient at the National Hospital for Neurology and Neurosurgery. Each patient was rated on the Krawiecka Manchester scale, a four point standardised psychiatric assessment scale for current positive and negative symptoms. The mean score for positive symptoms (incoherence, delusions, and hallucinations) was 2.0 and the mean score for negative signs (poverty of speech, flattened affect, and psychomotor retardation) was 2.2. The mean age of the patients was 38.5 (range 27–55). As a group, the patients with schizophrenia were chronically ill, with a mean duration of illness of 14.2 (SD 7.4) years. All patients except two were on medication with nine on neuroleptic drugs (mean dose 375.6 (SD 142.3) mg. Thirteen (five female, eight male) healthy normal subjects with no history of psychiatric or neurological illness, head injury, or drug misuse were tested. Their mean age was 38.15 (range 21–62). All subjects were right handed. To screen for cognitive deficits, the mini mental state examination was administered to all subjects. None of the subjects scored below the cut off point indicative of cognitive deficit.

PROCEDURE

Detailed descriptions of procedures are given by Brown et al. All subjects performed finger tapping and the Purdue pegboard task under unimanual, bimanual, and dual task conditions. In this task, subjects are required to place metal pegs (3 mm x 25 mm) in a vertical row of holes, as quickly as possible for a 30 second period. Subjects performed the task with each hand separately, and then bimanually. The number of unimanual and bimanual performance were the mean number of taps with the left and right hands under each condition. Subjects also performed a combined bimanual task. This involved tapping with one hand and placing pegs with the other. The task was performed twice, once with each hand-task combination each time for 30 seconds. The average of the two tests was calculated for each task. For all conditions the measures of bimanual performance were expressed as percentages of unimanual performance (for example, (PEGb/PEGu) x 100). In the combined task condition, subjects were instructed to perform both tasks at the same time as fast as they could and not to concentrate on one to the exclusion of the other.

The order of testing was randomised across subjects. All subjects were assessed on the Beck depression inventory (BDI). The mean ages of the two groups did not differ significantly (F(1, 23) = 0.032, p = 0.87). The mean of the MMS scores for the patients was 14.4 (SD = 10.3) and for the controls it was 4.5 (SD = 0.3). The difference between the two groups was significant (F(1, 23) = 6.35, p = 0.02). The mean score on the BDI for the patients was 28.2 (SD = 2.5) and for the controls 29.9 (SD = 0.3). The difference between the two groups was significant (F(1, 22) = 9.20, p < 0.01). The group differences in task performance were analysed both with and without MMS and BDI scores as covariates.

The table shows the mean performance of the two groups for each of the test conditions, as well as the performance of the bimanual conditions as a percentage of unimanual task performance. Also shown are the results of one way analyses of variance (ANOVA) and covariance (ANCOVA).

For the pegboard task, the patients with schizophrenia had significantly slower performance than the controls for the unimanual and bimanual tasks. The number of pegs placed in the bimanual condition as a percentage of the unimanual condition did not differ significantly between the two groups. Similar results were found for the tapping test. While tapping bimanually the patients were significantly slower than the controls and the difference approached significance (p = 0.06) for unimanual tapping. But when bimanual
tapping was considered as a percentage of unimanual performance, the two groups did not differ significantly.

Under dual task conditions of concurrent tapping and peg placement an interesting pattern of results emerged. The absolute numbers of pegs and taps were significantly different between the patients and the normal subjects, with the patients having fewer taps and placing fewer pegs in the dual task condition. The patients and controls also differed significantly in terms of percentage of change from the unimanual performance. However, relative to performance on the pegboard test alone, the patients with schizophrenia showed improved performance on the pegboard under the dual task condition, whereas the performance of the normal subjects was worse. Also, the patients with schizophrenia showed a significantly greater drop in tapping performance under dual task conditions than the normal subjects.

Under dual task conditions, for the pegboard task, we also examined the distribution of the absolute difference (pegs placed in bimanual task—pegs placed in unimanual dual task) for individual subjects in each group. This showed that peg placement in the dual task condition improved in 45%, remained constant in 27%, and deteriorated in 28% of the group with schizophrenia, whereas performance on the pegboard under the dual task condition improved in only 15%, remained constant in 8%, and deteriorated in 77% of the controls. These proportions were significantly different across the two groups ($\chi^2=5.92, df=2, p=0.05$). When the group differences in MMS and BDI scores were covaried out, only the group differences in the unimanual pegboard remained significant.

**Discussion**

The results show that patients with schizophrenia were significantly slower than the normal controls—they placed fewer pegs and had reduced tapping speed in unimanual and bimanual conditions. However, despite this overall slowness, the decrement in bimanual performance as a percentage of unimanual performance was not significantly different for the patients and controls on either the pegboard or tapping tasks. This suggests that although motor abnormalities such as poverty of action, perseverative movements, and motor slowness, reflected in slower reaction time and movement time in patients than in normal controls, have been reported in schizophrenia; patients with schizophrenia do not have major deficits in bimanual coordination. By contrast, in a previous study in Parkinson's disease, the patients showed greater decline in bimanual performance than normal subjects.

An interesting finding is that under dual task conditions, the performance of the patients with schizophrenia in peg placement actually improved relative to the unimanual pegboard task. The patients with schizophrenia were able to place more pegs while performing a secondary task with their other hand. By contrast, the tapping decreased compared with the unimanual tapping, a decrement that was significantly greater for the patients. Thus the improvement in the visually guided pegboard task was at the expense of the tapping task. Similar results have been found in patients with Parkinson's disease.

Previous studies have reported that patients with schizophrenia show impaired reaction times when a simultaneous cognitive task is introduced, thus suggesting limited attentional processing capacity. Why does performance on the visually guided task improve in patients with schizophrenia under dual task conditions? Brown and Jahanshahi provided alternative explanations for a similar improvement obtained in patients with Parkinson's disease. The first is that for each task there may be an optimal level of attention such that too much attention is detrimental to skilled performance. For example, thinking about individual movements can impair smooth motor planning and execution, such as when running down stairs; or golfers can greatly impair their putting by thinking about each single movement in the motor sequence. It is possible that under dual task conditions, by removing some of the "excess" attention, finger tapping makes the attentional allocation to peg placement optimal for the patients so that performance on the second task improves. The second explanation is that in the light of the deficits in schizophrenia in internal generation of action with relative normality of stimulus driven behaviour, rhythmical tapping acts as an external pacing cue that improves the visually guided pegboard. Thus it is possible that the patients are improving peg placement by using the rhythm of tapping as a pacing stimulus. Brown and Jahanshahi suggested that the first explanation can be tested by varying the cognitive load of a non-motor secondary task—for example, mental arithmetic—whereas the second explanation can be tested by manipulating the timing characteristics of the secondary tapping task. For patients with schizophrenia some evidence relating to these already exists. Granholm et al. used a visual search task, involving pointing at a screen when a target appeared as the primary task and a simple reaction time as the secondary task. Thus the primary task, although visually guided, had a less demanding motor output component than the pegboard task in this study, and the secondary reaction time task did not involve any rhythmic cueing. The patients with schizophrenia did not improve performance on the primary visual search task.
in the dual task condition but in fact showed a greater secondary task decrement (reaction time slowing) than controls in the highest processing load dual task condition. Therefore, in the present study it is more likely that the patients are using the rhythmic finger tapping as an external pacing cue to improve performance of the visually guided task.

There is evidence that, as suggested by Frith,\textsuperscript{29} patients with schizophrenia, especially those with high ratings of negative signs, are impaired in self generated but not externally triggered movements.\textsuperscript{26} Bimanual peg placement and tapping and peg placement under dual task conditions, were significantly associated with higher rates of negative signs, suggesting that patients with higher negative signs are more impaired under conditions in which the load on attentional capacity increases. The fact that covarying out MMS and BDI scores eliminated all significant differences between the patients and normal subjects suggests that the impairments in performance seen in the group with schizophrenia are associated with higher levels of depression and cognitive impairment.

In a recent review of evidence from various sources, Jahanshahi and Frith\textsuperscript{29} suggested that intentional or self generated actions (willed actions) are controlled differently from routine, stereotyped actions that are externally triggered by environmental stimuli. The authors also proposed that willed actions are controlled by a network of frontal cortical (dorsolateral prefrontal cortex, supplementary motor area, anterior cingulate) and subcortical (thalamus and basal ganglia) areas. Both Parkinson's disease and schizophrenia are characterised by symptoms such as akinesia or poverty of action and speech, deficits that reflect impairment of willed actions.\textsuperscript{25} Despite similarities, differences between patients with schizophrenia and Parkinson's disease are also evident. In our study of patients with Parkinson's disease an improvement for peg placement at the expense of tapping was seen, similar to that in the present study, but the patients with Parkinson's disease also showed greater impairment in the bimanual tasks than in the unimanual tasks compared with normal subjects; which was not found for the patients with schizophrenia.

The similarity in the dual task condition between the two patient groups with frontostriatal involvement,\textsuperscript{25}\textsuperscript{29} may reflect the greater dependence of both groups on visual signals and their reliance on rhythmic tapping as an external cue to improve peg placement.

In conclusion, the results of the current study showed, relative to normal subjects, a qualitatively different pattern of motor performance in patients with schizophrenia under dual task conditions which was associated with higher ratings of negative signs.

We thank Professor Maria Ron for allowing us to study patients under her care. The financial assistance of the Welcome Trust is gratefully acknowledged.

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Impairment of willed actions and use of advance information for movement preparation in schizophrenia

Rebecca Fuller, Marjan Jahanshahi

Abstract

Objectives—To assess willed actions in patients with schizophrenia using reaction time (RT) tasks that differ in the degree to which they involve volitionally controlled versus stimulus driven responses.

Methods—Ten patients diagnosed with schizophrenia and 13 normal controls of comparable age were tested. Subjects performed a visual simple RT (SRT), an uncued four choice reaction time (CRT), and a fully cued four choice RT task. A stimulus 1(S1)—stimulus 2(S2) paradigm was used. The warning signal/precue (S1) preceded the imperative stimulus (S2) by either 0 (no warning signal or precue) 200, 800, 1600, or 3200 ms.

Results—The patients with schizophrenia had significantly slower RTs and movement times than normal subjects across all RT tasks. The unwarned SRT trials were significantly faster than the uncued CRT trials for both groups. For both groups, fully cued CRTs were significantly faster than the uncued CRTs. However, the S1—S2 interval had a differential effect on CRTs in the two groups. For the normal subjects fully cued CRTs and SRTs were equivalent when S1—S2 intervals were 800 ms or longer. A similar pattern of effects was not seen in the patients with schizophrenia, for whom the fully cued CRT were unexpectedly equivalent to SRT for the 200 ms interval and unexpectedly faster than the 1600 ms S1—S2 interval, but not the 3200 or 800 ms intervals.

Conclusions—Patients with schizophrenia were able to use advance information inherent in SRT or provided by the precue in fully cued CRT to speed up RT relative to uncued CRT. However, in the latter task, in which the volitional demands of preprogramming are higher since a different response has to be prepared on each trial, patients showed some unusual and inconsistent interval effects suggesting instability of attentional set. It is possible that future studies using RT tasks with higher volitional demands in patients with predominance of negative signs may disclose greater deficits in willed action in schizophrenia.

Schizophrenia is a psychiatric disorder characterised by various symptoms. Positive symptoms are those that patients experience and by their presence distinguish patients from normal, such as thought disorder or hallucinations. Negative signs exist when the patients lack some element of normal behaviour—for example, flattening of affect, poverty of speech, and social withdrawal. Frith has suggested that the signs and symptoms of schizophrenia such as poverty of action or stereotyped action reflect a dysfunction of “willed” actions, whereas the processes involved in “stimulus driven” actions remain largely intact. This means that patients can perform routine acts elicited by environmental stimuli, but have difficulty in producing spontaneous behaviour in the absence of external cues.

One way of testing the hypothesis of impairment of willed actions in schizophrenia is to examine the speed of response initiation in reaction time (RT) tasks that differ in the extent to which they require volitionally prepared versus stimulus driven responses. In simple RT (SRT) tasks the same stimulus is presented across trials, and requires the same invariable response. The stimulus-response invariance provides the subject with the option of preparing the response before presentation of the stimulus—that is, to preprogramme it. In SRT, this preprogramming is an optional and volitional process, which has been shown to require attention as it is susceptible to interference from the concurrent performance of a secondary task. By contrast, in an uncued choice RT (CRT) task, in which there are several stimuli each indicating a different response, the response is elicited by presentation of the imperative stimulus. In uncued CRT, the response is selected and programmed after presentation of the stimulus, so it is considered to be stimulus driven. Volitional preprogramming is not possible in uncued CRT, but is a requirement in fully precued CRTs. In a fully cued CRT task a precue provides the subject with full advance information about the particular response required on that trial that allows its selection and preprogramming before the presentation of the imperative stimulus. The SRT and the fully cued CRT differ on one important factor: stimulus-response (S-R) variance. In the SRT the stimulus and response are the same on every trial, therefore the subject can preprogramme the same response for every trial. In the fully cued CRT, although full movement information is provided by the
Impairment of willed action in schizophrenia

precue, the subject must pre programme a
different response for each trial.

There have been studies of RTs in schizo-
phrenia since the 1930s. The most consistent
finding is that schizophrenic patients have sig-
nificantly slower RTs than normal controls. An-
other consistent finding is the "cross over effect" (COE), reported as far back as the
1940s. In normal subjects, in a simple RT
(task, if the interval between the warning
signal (S1) and imperative stimulus (S2) is
short (≤3 seconds), responses are initiated
faster on trials where the S1–S2 interval is kept
constant or blocked rather than presented ran-
domly across trials. This improved perfor-
mance is thought to be due to the temporal pre-
dictability of the imperative stimulus. However,
with longer S1–S2 intervals, normal subjects
have similar RTs regardless of whether the
S1–S2 intervals are random or blocked. Pati-
ents with schizophrenia generally show the
same RT benefit from temporal predictability
when S1–S2 intervals are short. By contrast,
when the S1–S2 intervals are longer, patients
with schizophrenia have slower RTs for the
blocked S1–S2 intervals than for the random
S1–S2 intervals. This phenomenon is called
the COE.

In the COE the patients with schizophrenia
are failing to use the advance information pro-
vided by the warning signal about the temporal
predictability of the imperative stimulus to
speed up the response. Few studies have exami-
ned the effect of other types of advance infor-
mation on RTs in schizophrenia—for example,
the use of advance movement parameter infor-
mation contained in a precue that allows
volitional preprogramming of the response
before presentation of the imperative stimulus.

Carnahan et al. measured RTs in leukot-
ominated and unleukotomised schizophrenic
patients compared with normal controls. Using
a version of Rosenbaum's paradigm, the
authors measured RT in uncued, partially
cued, and fully cued four choice RT (CRT)
conditions. The two schizophrenic groups were
slower than the normal subjects across all RT
conditions. The authors concluded that "the
leukotomised and the unleukotomised schizo-
phrenics were able to use this advance
information to facilitate the speed of their
responses in much the same way as did subjects
in a normal control group".

The type of information provided by a
preparatory signal (S1) presented before an
imperative stimulus (S2) can vary. Any signal
given a short time before an imperative stimu-
lus will serve as a warning to the subject, allow-
ing them to increase their level of alertness and
readiness to respond. This facilitation seems to
be optimal with a preparatory interval of 200
ms. Alternatively, the preparatory signal may
provide advance information about the nature of
the response itself—for example, it may
inform the subjects that they have to move to
the upper key with their right hand when the
imperative stimulus is presented. In this case it
may be referred to as a movement parameter
precue. This information potentially allows the
subject to preselect and pre programme a
specific response from a number of alterna-
tives, provided there is adequate time between
the precue and the imperative stimulus to take
action. The amount of reduction of RT by
warning stimulus and movement parameter
precues also depends on when they are pre-
presented relative to the imperative stimulus.
Therefore, the interval between the warning
signal/precue and the go signal is important in
determining the RT facilitation.

The aim of this study was to examine the
effects of different types of advance infor-
mation on RT in schizophrenia: (1) invariance
of the stimulus and response in SRT relative to
uncued CRT, (2) full advance movement
parameter information in a precued CRT task.

The study was designed to determine if the
interval between the warning stimulus/precue
(S1) and the imperative stimulus (S2) had
similar or differential effects on motor prepara-
tion in schizophrenic patients and normal sub-
jects.

Methods

SUBJECTS

The characteristics of the two samples are pre-
sented in the table. Ten subjects clinically diag-
nosed with schizophrenia according to the
DSM III R were tested. Each was seen as an
outpatient at the National Hospital for Neuro-
yology and Neurosurgery. Each patient was rated
on a four point standardised psychiatric assess-
ment scale for current positive and negative
symptoms. Overall, the patients were chroni-
cally ill and their symptoms were not very
severe. Thirteen healthy normal subjects with
no history of psychiatric or neurological illness,
head injury, or drug misuse were tested. The
mini mental state examination was adminis-
tered to all subjects and no one scored below
the cut off indicative of cognitive deficit.

PROCEDURE-REACTION TIME TASKS

A full description of the procedure is available
in Jahanshahi et al. Responses were made on a
response box with six buttons. The two centre
black buttons acted as the home keys. Four
inches above and 4 inches below each black
button were the response buttons. Stimuli were
presented on a 14 inch computer screen. A
variation of Rosenbaum's movement precue-
ing RT was used. The microsecond timer reset
the two home keys to begin the trial and a fixation
point appeared. The warning stimulus ap-
peared after a variable delay of 1–4 seconds.
The imperative stimulus (S2) appeared after
Tricyclic antidepressant drugs:
Anticholinergic drugs:
No medication (2)
Neuroleptic drugs:
Krawiecka scale (1977):
Mean duration of illness (y) 13.1 (7.0)
Mean mini mental state scores 28.0 (2.5) 29.9 (0.6)
Mean age (y) 37.9 (8.0) 38.9 (10.1)
Details of subject groups

<table>
<thead>
<tr>
<th>Sex</th>
<th>Patients with schizophrenia</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Male</td>
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<tr>
<td>Mean age (y)</td>
<td>37.9 (8.0)</td>
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<tr>
<td>Mean duration of illness (y)</td>
<td>13.1 (7.0)</td>
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</tbody>
</table>

Values in parentheses are SD.

Order of testing
The SRT condition was performed first followed by the CRT conditions. The order of performance of the CRT conditions was counterbalanced across subjects in each group. We considered counterbalancing more appropriate than randomising because for theoretical reasons we wanted subjects to perform SRT before the CRT tasks so as not to influence the S-R invariance of SRT by prior exposure to CRT with multiple stimuli and responses. Subsequently, we counterbalanced the order of testing of the CRT tasks.

Simple reaction time (SRT)
The stimulus and the response were constant across trials within a block. The subject moved from one home key to one response key, and all other keys were covered. Each subject performed two blocks of 50 trials (10 trials per interval), one block with each hand. The order of testing the left or right hand was counterbalanced across subjects in each group—that is, in the groups of patients with schizophrenia half of the subjects performed the test with their right hand first and half used their left hand first. Similarly, within the group of normal subjects the order of left and right hands was counterbalanced. At the end of the experiment, the SRT condition was presented again to assess possible fatigue or practice effects. Within a block of 50 trials, S1-S2 intervals of 0, 200, 800, 1600, and 3200 ms were randomly presented, 10 trials each.

Four choice reaction time (CRT)
There were two movement parameters, hand (right or left) and direction (up or down). The two conditions were either uncued or fully cued. In each condition there were 75 trials with 15 trials of each of the five S1-S2 intervals randomly mixed in a block. A similar and randomly mixed number of right and left hand responses were incorporated.

Uncued CRT
The warning stimulus consisted of four empty squares appearing to the left and right and above and below the fixation cross. After the S1-S2 interval one square filled which became the imperative stimulus.

Fully cued CRT
One empty square appeared in one of the four possible locations above or below, to the left or right of the fixation point. After the S1-S2 interval the square filled to become the imperative stimulus. Thus the subject knew the precise nature of the required response before the presentation of the imperative stimulus.

STATISTICAL ANALYSIS
Mean RTs were used for further analysis. The data were analysed using the Statistical Program for Social Sciences (SPSS), version 8.0. Differences between RTs for the left versus right hand were examined using repeated measures analysis of variance (ANOVA) with group as the between subjects factor and hand (left, right), condition (SRT, uncued CRT, fully cued CRT), and S1-S2 Interval (0, 200, 800, 1600, 3200 ms) as the within subject factors. For both groups, although RTs for the right hand were (non-significantly) faster than those for the left hand, there were no interaction effects of hand with any other variable (group, condition, S1-S2 interval). The data for the left and right hands were averaged for each condition. This average was used in all subsequent analyses.

t Tests were used to further investigate significant interactions in the ANOVAs. When t tests were used equal variances were not assumed. Paired t tests were used to examine within subject measures and independent t tests were used for between group measures.

To compare the difference between the true SRT and CRT conditions, data from the trials with an S1-S2 interval of 0 ms—that is, without a warning signal, were analysed using a repeated measures ANOVA. The between subject factor was group (patients, controls) and the within subject factors were condition (SRT (0 ms S1-S2 interval) and uncued CRT(0 ms S1-S2 interval)).

To examine the effects of advance movement parameter information on CRT, the differences between the uncued and fully cued CRT were
The two groups did not differ in age (r=0.25, Whitney U tests for the between groups comparisons and Wilcoxon matched pairs test for the within subject analyses).

Results

The two groups did not differ in age (r=0.25, df=21, p=0.80) or male to female ratio (X^2=0.25, df=1, p=0.62). Although the groups differed on scores on the mini mental examination (r=2.5, df=21, p=0.05), no subject scored below the cutoff of 25.

Fatigue or practice effects were assessed by comparing SRTs performed at the beginning and end of the session. The controls had a mean RT of 351 (SD 57) ms for the first SRT and a mean RT of 373 (SD 63) ms for the final SRT, a mean difference of 22 (SD 33) ms. The mean RT of the patients with schizophrenia was 442 (SD 105 ) ms for the first SRT and 474 (SD 104) ms for the final SRT, a mean difference of 17 (SD 21) ms. There was no significant difference between the change in RT between the two groups (r=0.41, df=20, p=0.69).

ERROR DATA

Very few errors of any type were made by the patients or normal subjects. In the SRT for the schizophrenic group, the median number of anticipation errors was 0.10 (range 0.00-0.80) and the median number of long responses was 0.00 (range 0.00-1.00). For the controls, the median number of anticipation errors was 0.10 (range 0.00-0.40) and the median number of long responses was 0.00 (range 0.00-0.40). Across the SRT conditions, the schizophrenic group had a median of 0.10 (range 0.00-3.50) anticipation errors, 0.00 (range 0.00-0.30) long responses, and 0.10 (range 0.00-0.10) decision errors. Across the CRT conditions, the controls had a median of 0.01 (range 0.00-0.20) anticipation errors, 0.00 (range 0.00-0.15) long responses, and 0.00 (range 0.00-0.20) decision errors.

A series of Mann-Whitney U tests showed that there were no significant differences between the patients and controls in the number of anticipations, decision errors, or long responses in the various RT conditions (p>0.05). Similarly, Wilcoxon matched pairs tests showed that there were no differences in errors between the various RT conditions for the patients with schizophrenia (p>0.05). For the controls, there were more anticipation errors in the SRT compared with the uncued CRT (Z=2.5, p=0.01) but not in the fully cued CRT (Z=1.21, p=0.22) conditions. Also, for the controls there were more anticipation errors in the fully cued CRT than in the uncued CRT (Z=2.6, p=0.01).

UNCUED CRT VERSUS FULLY CUED CRT

The mean RTs for the two groups in unwarned CRT and unwarned and uncued CRT conditions are presented in figure 1. The group effect was significant (F(1,20)=7.94, p=0.01) with patients with schizophrenia having slower reaction times than the controls. The condition effect was significant (F(1,20)=18.16, p=0.001) with SRTs being faster than CRTs; however the group×condition interaction was not significant (p>0.1). To determine if the speeding up of SRT relative to CRT which is an index of preprogramming was equivalent in the two groups, the differences in RT between the two conditions were examined using paired t tests for each group. The mean differences between the CRT and SRT conditions was 60.3 (SD 50.6) ms for the controls and 69.1 (SD 91.8) ms for the patients with schizophrenia. The unwarned SRT was significantly faster than the uncued and unwarned CRT for both the controls (t=4.30, df=12, p=0.01) and the patients with schizophrenia (t=2.30, df=8, p=0.05).
contrast, the condition×interval ($F(3, 63)=5.18$, $p=0.003$), the group×interval ($F(3, 63)=4.84$, $p=0.004$) and the group×condition×interval ($F(3, 63)=4.29$, $p=0.01$) interactions were significant.

Further analysis of the condition effect showed that across the two groups and the various intervals, the uncued CRT was significantly slower than the fully cued condition ($p=0.001$). The significant main effect of interval was also examined in more detail. Across the two groups, RTs for the 800 ms S1–S2 interval were slower than those for the 200 ms ($p=0.001$), the 1600 ms ($p=0.001$) and the 3200 ms ($p=0.001$) intervals. No other intervals differed significantly.

Further analysis of the group×interval interaction showed that for the control subjects RTs for the 3200 ms intervals were faster than those for the 200 ms ($p=0.04$) and the 800 ms interval ($p=0.002$). By contrast, for the patients with schizophrenia RTs for the 800 ms interval were slower than those for the 200, 1600, and 3200 ms intervals ($p<0.01$) and no other intervals differed ($p>0.05$).

Further analysis of the group×condition×interval interaction disclosed that across the two CRT tasks for the controls subjects fully cued CRT were significantly faster than the uncued CRT at each interval (200, 800, 1600, and 3200 ms) ($p<0.02$). On average for the normal subjects, the fully cued CRT was faster than the uncued CRT by 19.9, 83.1, 68.7, and 73.4 ms respectively with the 200, 800, 1600, and 3200 ms S1–S2 intervals. Thus the differences between the two CRT conditions at the 200 ms interval, although small (mean 19.9 (SD 24.5) ms), reached significance. For the patients with schizophrenia the RTs for the fully cued CRT were significantly faster than the CRTs for the uncued CRT for the 1600 ms (faster on average by 86 ms) and 3200 ms (faster on average by 77.4 ms) intervals ($p<0.01$) only.

SRT VERSUS FULLY CUED CRT

The mean RTs for the two groups for the SRT and fully cued CRT are shown in figure 3. The main effects of group ($F(1, 20)=7.60$, $p=0.01$), condition ($F(1, 20)=12.19$, $p=0.002$), and interval ($F(3, 60)=11.89$, $p=0.001$) were significant. The group×condition interaction ($F(1, 20)=2.35$, $p=0.14$) was not significant. The condition×interval ($F(3, 60)=2.80$, $p=0.05$), group×interval ($F(3, 60)=3.43$, $p=0.02$), and the group×condition×interval ($F(3, 60)=9.52$, $p=0.01$) interactions were significant.

The significant three-way interaction was examined further by investigating differences between SRT and fully cued CRT for each of the four intervals within each group. For the normal subjects, fully cued CRTs were significantly slower than SRTs at the 200 ms interval ($p=0.001$) but not at the 800, 1600, or 3200 ms intervals ($p>0.1$). By contrast, for the patients with schizophrenia, CRTs were significantly faster than the uncued CRT by 19.9, 83.1, 68.7, and 73.4 ms respectively with the 200, 800, 1600, and 3200 ms S1–S2 intervals. Thus the differences between the two CRT conditions at the 200 ms interval, although small (mean 19.9 (SD 24.5) ms), reached significance. For the patients with schizophrenia the RTs for the fully cued CRT were significantly faster than the CRTs for the uncued CRT for the 1600 ms (faster on average by 86 ms) and 3200 ms (faster on average by 77.4 ms) intervals ($p<0.01$) only.
Impairment of willed action in schizophrenia

slower than SRTs for the 800 (p=0.01) and the 3200 ms interval (p=0.04) but not for the 200 or the 1600 ms S1-S2 intervals (p>0.1).

MOVEMENT TIME
The main effects of group (F(1,20)=8.29, p=0.01) and condition (F(2,31)=10.67, p=0.001) were significant, but not the main effect of interval (F(3,54)=1.94, p=0.14). There were no significant interaction effects (p>0.05). The patients with schizophrenia had slower MTs (278 (SD 68) ms) than the controls (190 (SD 73) ms). MTs were significantly faster in the SRT condition compared with each CRT condition (p<0.05). The two CRT conditions did not differ.

Discussion
Overall, the RTs and MTs of patients with schizophrenia were significantly slower and more variable than those of age matched normal subjects across all conditions. Unwarned SRT were significantly faster than the uncued CRT in both groups. For both groups the fully cued CRTs were significantly faster than the uncued CRTs. There was a curious interval effect for the patients with schizophrenia which resulted from the fact that in the fully cued CRT condition, the patients with schizophrenia had CRTs which were significantly faster at the 200 ms than the 800 ms interval. Besides significant slowness in movement initiation and execution, significant differences in interval effects were the main factors that distinguished the various RTs of the patients and controls.

Before we discuss the main results further we will consider and exclude the possible effects of confounding factors on the RT results. As it was not possible to test the patients with schizophrenia not taking medication, there is always the possibility that the results obtained are affected by the medication that eight of the 10 patients were taking. Most existing studies have found no effect of neuroleptic medication on RTs. Nevertheless, in an RT paradigm with auditory stimuli, RTs were significantly lower for schizophrenic patients on medication than in those not taking medication. Whereas the first results suggest that medication status may not affect RTs, the second study suggests that the slowing of RTs in schizophrenia may be partly attributable to the neuroleptic medication that is taken by most patients. If this is the case, then RTs should be assessed in drug free patients, a procedure which is not feasible in most studies for clinical reasons. In the present study, there was some indication that the RTs of the two patients who were not taking any medication at the time of the study were in fact somewhat slower than those of the remaining eight patients taking medication.

For both groups, RTs slowed slightly during the experiment as seen by the increased RT in the final SRT task compared with the initial SRT task. As there was no significant difference between the two groups on the amount of slowing, the results are not confounded by different patterns of fatigue effects in the two groups.

Precuing produced no differential effect on MT, as MTs for uncued and fully cued conditions did not differ significantly. By contrast, precuing or provision of advance movement parameter information, produced a significant effect on RTs. The RTs were significantly faster for the fully cued than for the uncued CRT. The differential effects of precuing on MTs and RTs suggest that the use of advance information for motor preparation is complete by the end of the RT period when the subject lifts his or her index finger from the home key and that there is no evidence of "on line" preparation during movement execution.

The two groups did not differ in the number of anticipations, decision errors, or long responses. Therefore, the differences in RT between the patients with schizophrenia and normal subjects do not seem to be associated with different speed-accuracy trade offs across the two groups.

USE OF STIMULUS RESPONSE INVARINCE FOR PREPROGRAMMING IN SRT: SRT VERSUS UNCUED CRT
The patients with schizophrenia were significantly slower than the controls on both the SRT and uncued CRT tasks. However, for both groups the SRT was significantly faster than CRT. These results suggest that in the SRT condition, which involves optional and volitional preprogramming, the patients with schizophrenia preprogramme the response before presentation of the stimulus. As a result this condition was significantly faster than the uncued and unwarned CRT, which is a purely stimulus driven task in which no preprogramming is possible and the correct response is selected, prepared, and initiated only after presentation of the imperative stimulus. The significant slowness of SRT in schizophrenia relative to normal subjects agrees with the results of previous studies. Nuechterlein has reviewed the few studies which have directly compared SRT and uncued CRT in schizophrenia. As with the present results, all previous studies have found that CRT is slower than SRT for patients with schizophrenia, similar to normal subjects. However, the present results also showed that the CRT>SRT difference was similar in the two groups.

USE OF ADVANCE MOVEMENT PARAMETER INFORMATION FOR PREPROGRAMMING IN CRT: FULLY PRECUED VERSUS UNCUED CRT OR SRT
The fully cued CRTs were significantly faster than the uncued CRTs for the patients with schizophrenia, similar to the normal subjects. This is in agreement with previous studies suggesting that valid cues are used by patients with schizophrenia to speed up RT. However, the significant groupxinterval and group xconditionxinterval interactions when comparing the fully cued CRT with the uncued CRT or SRT, disclosed that the patients with schizophrenia showed anomalies in the use of advance information. Confirming our previous finding for the normal subjects with the RT tasks used, an S1−S2 interval of 200 ms is not long enough for subjects to use advance information to speed
up fully cued CRTs to the level of SRTs. But with S1–S2 intervals of 800 ms or longer, the advance information provided by the precue is fully used by normal subjects to speed up precue CRTs and make these equivalent to the corresponding SRTs. For the patients with schizophrenia an unusual S1–S2 interval effect was present, mainly due to slower fully cued CRTs for the 800 ms and faster fully cued CRTs for the 200 ms S1–S2 interval. As a result, by contrast with the normal subjects, fully cued CRTs were equivalent to SRT even for the 200 ms interval, but not for the longer 800 ms S1–S2 interval or the 3200 ms interval. Examination of the raw data shows that the interval effect found was not caused by a single outlier. Nine of the 10 patients had slower fully cued CRTs for the 800 ms S1–S2 interval relative to the 200 ms S1–S2 interval. This abnormal S1–S2 interval effect may reflect inconsistencies of set in patients with schizophrenia similar to that seen in the cross over effect.  

There are some similarities between the current results for patients with schizophrenia and results from patients with Parkinson’s disease in our previous study. Both patient groups had significantly slower RTs and MTs than age matched normal subjects, both were able to use the S–R invariance to preprogramme the response in SRT and use advance information in precued CRT tasks to speed up their RTs relative to uncued CRT. However, both groups showed abnormal interval effects. Patients with Parkinson’s disease required a longer S1–S2 interval (2000 ms) to speed up fully cued CRTs to the level of SRT whereas elderly normal subjects did so with an S1–S2 interval of 800 ms. In the present study, instability of attentional set in schizophrenia was associated with equivalent RTs for the fully cued CRT and SRT for the 200 ms and 1600 ms S1–S2 interval but not the 800 or 3200 ms S1–S2 intervals.

DEFICITS IN VOLITIONAL PROCESSES IN SCHIZOPHRENIA

The extent to which actions are volitional or reflexive differ on a continuum from the completely automatic and reflexive such as the knee jerk, to the fully internally driven such as spontaneous actions. Most of our daily actions rest somewhere in between. This is also true of the various RT tasks used in the present study, which differed in the degree of volitional control required for selection, preparation, and initiation of a response. The uncued CRT task was probably the least demanding of volitional control. For this reason, the patients with schizophrenia showed no significant differences in uncued CRTs relative to the normal subjects. The SRT task would probably be placed next on a continuum of degree of volitional control required. The optional but internally driven preprogramming in the SRT task is dependent on an action that is "automatic", in contrast with the stimulus–response pairing never varies, the subject preprogrammes the same response on each trial. There was evidence that the patients with schizophrenia were engaging in this.

Finally, in the fully precued CRT, as the imperative stimulus repeated the information held in the precue, preprogramming was also optional and volitional and the subject could simply wait for the imperative stimulus before programming the response similar to uncued CRT. However, in the fully cued CRT although the exact response is known before presentation of the imperative stimulus, the subject must preprogramme a different response for each trial. Thus a higher degree of volitional control is required relative to SRT, where given the S–R invariance, the same response is preprogrammed across trials in a block.

Performance of SRT tasks concurrently with a second attention demanding task under dual task conditions, which introduces a capacity load and requires greater volitional control, has been shown to be particularly detrimental to the performance of patients with schizophrenia. In general, evidence suggests that patients with schizophrenia are particularly slowed by increases in task complexity in CRT tasks. For example, in a review of the literature on information processing in schizophrenia, Hemsley (D R Hemsley, unpublished PhD thesis 1976) concluded that CRT tasks involving low S–R compatibility are more sensitive to deficits in schizophrenia. There is some suggestion from the present results that in schizophrenia RT deficits become more evident as tasks require greater volitional control. As noted above, compared with SRT where the same response is preprogrammed across all trials, in fully cued CRT, a different response has to be preprogrammed on each trial, hence requiring greater allocation of attention and volitional control. It was precisely on the fully cued CRT condition that the patients with schizophrenia showed unusual and inconsistent interval effects suggesting instability of attentional set. These unusual interval effects are reminiscent of the cross over effect, which has been replicated in schizophrenia in numerous studies. The cross over effect has also been interpreted as reflecting an impaired ability to maintain attentional set. Such instability of attentional set may contribute to other deficits found in schizophrenia such as increased perseveration on the Wisconsin card sorting test or the modality shift effect. Therefore, the present results suggest that ordinarily, the patients with schizophrenia do not have any major deficits in preprogramming of responses in an SRT or a fully cued CRT task. However, in the second task, in which the volitional demands of preprogramming are higher as a different response has to be prepared on each trial, patients show some unusual and inconsistent interval effects suggesting instability of attentional set. In the present study, it was not possible to differentiate subgroups of patients with predominance of negative signs or positive symptoms. It is possible that future studies using RT tasks requiring greater volitional control (for example, with high stimulus-response incompatibility requiring volitional S–R decoding before response selection) and a sample of patients
with schizophrenia and predominance of negative signs may show greater deficits in willed action.

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Movement-related potentials prior to self-initiated movements are impaired in patients with schizophrenia and negative signs

Rebecca Fuller • David Nathaniel-James • Marjan Jahanshahi

Abstract It has been suggested that certain symptoms of schizophrenia such as poverty of action and speech, and stereotyped action, reflect a dysfunction of "willed" actions while the processes involved in "stimulus-driven" actions remain intact. The aim of this study was to test this hypothesis by measuring movement-related potentials (MRPs) prior to self-initiated and externally triggered movements in three groups of subjects: five patients with a diagnosis of schizophrenia with high ratings of negative signs, six patients with a diagnosis of schizophrenia with high ratings of positive symptoms, and six normal controls. Subjects lifted their right index finger at an average rate of once every 3 s in two conditions, either as self-initiated movements, or as a response to a tone while MRPs were recorded from frontal, frontocentral, central, and parietal sites. The patients with schizophrenia and high ratings of negative signs had reduced amplitude of MRPs for the late and peak component and reduced slope of the early and late MRPs prior to self-initiated movements. These differences were not found prior to externally triggered movements. The patients with schizophrenia with high ratings of positive symptoms did not differ significantly from the normal controls in terms of amplitude or slope of MRPs prior to self-initiated or externally triggered movements. These deficits in willed actions may be mediated by impaired functioning of the frontostriatal loops.

Key words Schizophrenia • Willed action • Movement-related potentials (MRPs) • Bereitschaftspotential • Motor preparation • Negative signs

Introduction

Movement-related potentials (MRPs) are electrophysiological measures recorded over the scalp, which reflect preparatory processes prior to movement. The Bereitschaftspotential (BP) is a negative MRP occurring 1–1.5 s prior to a self-paced movement (Kornhuber and Deecke 1965). The BP is considered to consist of three components, the early BP, with onset 1–1.5 s prior to the movement onset, the late BP, which occurs about 500 ms prior to movement onset, and the peak BP, which either coincides with or occurs about 50 ms prior to the onset of movement (Deecke et al. 1969, 1976).

Libet et al. (1982, 1983) suggested that two volitional processes contribute to the BP. The first, which in terms of its timing corresponds to the early component, is considered to reflect volitional motor preparatory processes associated with the development of preparation to act in the near future. The second, which in terms of its timing corresponds to the late component, is associated with voluntary choice and with the endogenous 'urge' or intention to act. With self-paced or self-initiated movements the early, late, and peak BP components are present (Kutas and Donchin 1980; Thickbroom et al. 1985; Papa et al. 1991; Aminoff et al. 1993; Jahanshahi et al. 1995); reflecting the preparation involved in planning to move, as well as the endogenous intention to act (Jahanshahi et al. 1995). Previous studies have shown that with externally triggered movements if the stimulus occurs regularly and can be anticipated, motor preparation is possible and some pre-movement negativity is present (Kutas and Donchin 1980; Thickbroom et al. 1985; Papa
et al. 1991; Aminoff et al. 1993; Jahanshahi et al. 1995). With regularly triggered movements, however, the decision when to move is not self-generated, but is determined by the onset of the triggering stimulus. Therefore, it can be suggested that the late component in a regularly paced externally triggered movement is lower than in a self-initiated movement because the late component reflects only the maintenance of motor preparation without volitional decision-making about when to act (Jahanshahi et al. 1995). With externally triggered movements, if stimulus presentation is irregular and its onset cannot be anticipated and motor preparation is not as viable, then there is no pre-movement negativity, only the final activation of the motor cortex seen in the peak BP (Aminoff et al. 1993; Jahanshahi et al. 1995).

Several studies have investigated the BP in schizophrenia and found impaired BPs compared to normals (Bachneff and Engelsman 1983; Chiarenza et al. 1985; Singh et al. 1992; Karaman et al. 1997). However, the results of these studies are contradictory. For example, while some previous studies have found both the early and late BP to be reduced in schizophrenia (Singh et al. 1992), others report the early BP to be reduced in patients with positive symptoms and the late BP to be reduced in patients with negative signs (Karaman et al. 1997). There have also been reports that medicated patients with schizophrenia with tardive dyskinesia have larger BP amplitude compared to controls while patients with schizophrenia without tardive dyskinesia do not differ from normals (Adler and Nagamoto 1989). While some studies have shown a longer BP duration in schizophrenia (Westphal et al. 1996), others reported a shorter BP duration in schizophrenia which was found to be associated with flattening of affect (Bachneff and Engelsman 1983).

On theoretical grounds impairment of BPs would be expected in patients with predominantly negative signs. Frith (1992) has suggested that the negative signs of schizophrenia such as poverty of action, poverty of speech and social withdrawal reflect a dysfunction of willed actions. Willed actions are self-selected or self-initiated voluntary movements. The precise nature or timing of these actions is decided by the individual rather than determined by external stimuli (Jahanshahi and Frith 1999). One way to test this hypothesis of impairment of willed actions in patients with schizophrenia and a predominance of negative signs is to compare MRPs prior to self-initiated and externally triggered movements in three groups: normal controls, patients with schizophrenia ranking high on positive symptoms, and patients with schizophrenia ranking high on positive symptoms. We predicted that the main differences would be found between the normals and patients with negative signs prior to self-initiated movements and that fewer or no group differences would be evident for MRPs prior to externally triggered movements or the group with predominantly positive symptoms compared with the normals.

Materials and methods
Design
A mixed between-groups and within-subject design was used. Three groups of subjects took part in the experiment: normal controls, patients with schizophrenia with high ratings of positive symptoms and patients with schizophrenia with high ratings of negative signs. There were three experimental conditions (self-initiated, externally triggered, and rest).

Subjects
Table 1 shows the characteristics of the samples. Thirteen patients diagnosed with schizophrenia according to DSM IV were recruited from the National Hospital for Neurology and Neurosurgery. The data of two patients were excluded, one because of excessive movement and one due to excessive electro-oculogram (EOG) artifact. The data from the remaining 11 patients were used in the analysis. Each patient was rated on a four-point standardised psychiatric assessment scale (Krawieka et al. 1977) for current positive symptoms and negative signs. Those subjects who had a higher rating of positive symptoms (incoherence, delusions and hallucinations, maximum total score=12) compared to negative signs (poverty of speech, flattened affect and psychomotor retardation, maximum total score=12) were placed in the ‘positive’ group (four male, two female). Those with a higher negative compared to positive score were placed in the ‘negative’ group (five male). For both groups, the mean scores for positive symptoms and negative signs differed significantly (P<0.05). The two groups did not differ significantly in terms of duration of illness (P>0.05).

Two patients in the positive schizophrenia group were not on medication, while all other patients were. The two groups did not differ significantly for mean dose of anticholinergic or neuroleptic medication (P>0.05). Seven healthy normals with no previous history of psychiatric or neurological illness, head injury, or drug abuse were tested. One normal subject’s data were excluded due to excessive EOG artifact. The data from the other six normals (one male, five female) were used for analysis. To screen for cognitive deficits, the Mini Mental State Examination (Folstein et al. 1975) was administered to all subjects. None of the subjects scored below the cut-off of 25, indicative of cognitive deficit. All subjects were right handed except for one (positive schizophrenia group), who was ambidextrous. The three groups were matched on age and handedness (Oldfield 1971) and did not differ in terms of scores on the Beck Depression Inventory (BDI) (Beck et al. 1961) or the Mini Mental State Examination (MMSE) (P>0.05). The three groups did differ in terms of proportion of males to females (χ²=8.06, d.f.=2, P=0.02).

Procedure
Informed consent was obtained from all subjects. MRPs were recorded in three experimental conditions:

1. Self-initiated movements: subjects made self-initiated movements at an average rate of once every 3 s. The movement involved a brisk lifting of the right index finger. The subject's finger rested on a zero force touch switch. Extension of the finger interrupted contact with the switch. Interresponse intervals were measured to the nearest millisecond. A tone, which subjects were told to ignore, was presented 100 ms after the self-initiated movement. This was to control for the tone effect in the externally triggered condition.

2. Externally triggered movements: subjects made the same finger-lifting movement in response to a tone presented at an identical rate to that generated by the subjects in the self-initiated condition: i.e. the rate of movement was yoked to that generated by the subject in the self-initiated condition. This
was achieved by saving the interresponse intervals produced by the subject in the self-initiated condition on the computer, which were then used as the interstimulus intervals for presentation of the tone in the externally triggered and rest conditions. Reaction times (time from presentation of tone to subject lifting finger) were measured to the nearest millisecond.

3. Rest: subjects listened to tones presented at a rate yoked to condition (1). No response was required. This condition was included to control for the sensory potentials evoked by the tone in condition (2).

Because of the necessity of yoking the rate of tone presentation to the rate of self-initiated movements, a fixed order was used. In each block, subjects performed the self-initiated condition, then the externally triggered condition, followed by the rest condition. Four blocks of 60 trials of each condition were performed.

Recording of MRPs

The subject sat in a comfortable reclining chair in a quiet, dimly lit room. All recordings were made with Digitimer D150 amplifiers. The EEG was recorded using non-polarizable Ag/AgCl electrodes. The electrode positions were a modification of the International 10-20 convention, with placements at F3, Fz, F4, FC3, FCz (4 cm anterior of vertex), FC4, C3, Cz (vertex), C4, P3, Pz, P4. Electrodes were secured to the scalp with collodion. Linked earlobes served as the reference. The subject was grounded on the left wrist. The high frequency cut-off was set at 100 Hz; the low-frequency cut-off was 0.03 Hz, with a time constant of 5 s. The EOG was recorded from electrodes placed at the glabella and on the outer canthus of the right eye. For recording of EOG the high-frequency cut-off was set at 100 Hz; the low-frequency cut-off was 0.03 Hz, with a time constant of 5 s. The EOG was thus not interfering with the movement-related components of interest. For EMG recording a high-frequency cut-off of 3 kHz, a low-frequency cut-off of 53 Hz, and a time constant of 1.6 s were used. The EMG was rectified and integrated and was used for back-averaging of the EEG on a trial-by-trial basis. The minimum number of valid trials was 100.

Analysis of MRPs

In the externally triggered condition, all measurements were obtained from the subtracted waveforms: i.e. traces from which the sensory components (Nd, Qd, Pqd) elicited to the tone alone in the rest condition had been subtracted to obtain a 'pure' measure of movement-related negativity. This subtraction process involved a number of steps. First, for each subject, the sensory components to the tone in the rest condition were reworked by offsetting them with the reaction time of the subject on a trial-by-trial basis. Thus, the potentials evoked by the tone were spread by the variability of the subject’s reaction time. Then the onset of the tone in the triggered condition was superimposed on the onset of the tone in the reworked rest condition, which aligned the sensory components in the two conditions. Finally the EEG data were subtracted, leaving the pre-movement potentials in the two externally triggered conditions without the sensory components due to tone. The movement-related components preceding the movement onset, which were of primary interest, were not altered by the subtraction process, which simply subtracted the negativity associated with the presentation of the tone trigger. This procedure was not carried out using the self-initiated data since the tone was present after EMG onset and was thus not interfering with the movement-related components of interest.

For scoring the BP prior to the self-initiated movements, procedures similar to those previously employed in our laboratory (Dick et al. 1987, 1989; Jahanshahi et al. 1993) were used. Only the three pre-movement components of the MRPs, i.e. the early, late and peak BPs, were measured. To determine the onset of each of the three components, printouts of the averaged waveform for each subject and each type of movement were examined indepen-

Table 1 The characteristics of the three samples. Values given are means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Positive schizophrenia</th>
<th>Negative schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44 (14.3)</td>
<td>42 (7.9)</td>
<td>38 (4.6)</td>
</tr>
<tr>
<td>Mini Mental State Examination (0-30)</td>
<td>30.0 (0.0)</td>
<td>28.5 (2.0)</td>
<td>29.2 (1.3)</td>
</tr>
<tr>
<td>Beck Depression Inventory (max -63)</td>
<td>9.3 (3.6)</td>
<td>14.2 (12.6)</td>
<td>11.2 (8.4)</td>
</tr>
<tr>
<td>Handedness (-100=purely left handed, 100=purely right handed)</td>
<td>75 (18.0)</td>
<td>77 (14.0)</td>
<td>90 (8.9)</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>17.2 (8.2)</td>
<td>12.0 (2.7)</td>
<td>1.0 (1.7)</td>
</tr>
<tr>
<td>Positive symptoms (hallucination, delusions, incoherence) (0-12)</td>
<td>6.7 (4.0)</td>
<td>1.0 (1.7)</td>
<td>6.7 (4.0)</td>
</tr>
<tr>
<td>Negative signs (poverty of speech, flattened affect, psychomotor retardation) (0-12)</td>
<td>2.8 (3.8)</td>
<td>4.4 (4.4)</td>
<td>2.8 (3.8)</td>
</tr>
<tr>
<td>Dose anticholinergic (Disipal equivalent)</td>
<td>50.0 (54.8)</td>
<td>80.0 (130.4)</td>
<td>50.0 (54.8)</td>
</tr>
<tr>
<td>Dose neuroleptic (chlorpromazine equivalent)</td>
<td>128.3 (123.3)</td>
<td>316.0 (295.9)</td>
<td>128.3 (123.3)</td>
</tr>
</tbody>
</table>

onset). For the rest condition, where there was no response, the tone acted as the trigger for sampling the EEG data. The analogue data were digitized to 12-bit resolution using a CED-1401 general purpose laboratory interface (Cambridge Electronic Design, Cambridge, UK 1988). Data collection was controlled using the SigAvg programmes (version 6.03; Cambridge Electronic Design 1993). Prior to off-line analysis of the MRP data, any remaining trials with EOG or movement artifact were eliminated and the records were back-averaged using the EMG onset on a trial-by-trial basis.
dently by three scientists who had experience with BPs. For each record, the point of onset of the early, late and peak BP components were marked using Cz as the main reference trace. The onset of each component for each subject and each type of movement was determined by taking the consensus point. Using the marked points, the mean latency of the early BP (rise of the slope from baseline), the late (point of change in slope) and the peak BP (most negative point at or prior to EMG onset) onset were measured in relation to EMG. The amplitudes of the early and peak BP were measured, and using these values the amplitude of the late BP was calculated through subtraction. Amplitudes were measured in relation to a 300-ms baseline which was obtained by averaging the traces between the point of onset of the early BP and the preceding 300 ms. The onset of the early and late components was not clear in every trace for the externally triggered waveforms. Therefore, the points of onset of the early and late components from the self-initiated data were used to mark the onset of these components in the externally triggered waveforms for all subjects. The peak BPs, however, were clearly visible in the externally triggered data, so these points were marked for each subject's trace.

The slope of the early component was measured between the point of onset of the early BP and the onset of the late BP. The slope of the late component was measured from the point of onset of the late BP to the onset of the peak BP. The slopes were measured in microvolts per second.

The data for each component of the MRP (early, late and peak) were analysed separately for the self-initiated and the externally triggered responses using repeated measures analysis of variance (ANOVA). In each ANOVA, Group (normals, patients with positive symptoms, patients with negative signs) was the between subject variable and Electrode Site (F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, P3, Pz, P4) was the within-subjects repeated measures variable. The slope of the early BP and the slope of the late BP were also analysed using similar repeated measures ANOVA. Where necessary, to deal with violations of assumptions of sphericity, the Greenhouse-Geisser epsilon was used to adjust the degrees of freedom. Pre-planned special contrasts were carried out using SPSS for Windows version 8.0.

Results

Behavioural data

Mean interresponse intervals for the self-initiated condition and reaction times for the externally triggered are presented in Table 2. The three groups did not differ significantly for the interresponse intervals \( F_{(2,14)} = 1.58, P = 0.24 \) or reaction times \( F_{(2,14)} = 1.01, P = 0.37 \). The important aspect of the behavioural data is that all three groups produced self-initiated movements at the target rate of on average once every 3 s. Since the rate of movement for the externally triggered condition was yoked to the self-initiated condition, this means that the three groups did not differ in terms of the rate of movement in the triggered condition either.

Latencies

Table 3 contains the latencies for each group. For the self-initiated movements, there were no significant differences among the three groups for latencies of the early \( F_{(2,14)} = 1.88, P = 0.19 \), late \( F_{(2,14)} = 0.55, P = 0.59 \), or peak \( F_{(2,14)} = 0.01, P = 0.99 \) BP. For the externally triggered movement the latency of the peak BP did not differ significantly among the three groups \( F_{(2,13)} = 1.51, P = 0.26 \).

Amplitudes

The waveforms of the MRPs prior to the self-initiated and externally triggered movements are shown in Figs. 1 and 2. The waveforms of the MRPs preceding self-initiated movements for the one patient from the ‘positive’ group with the highest level of medication and one patient from the ‘negative’ group with low levels of medication are presented in Fig. 3.

MRPs prior to the self-initiated movements

For the early component the main effects of Group and Electrode Site and the GroupxElectrode Site interaction were not significant \( P > 0.05 \). For the late component the main effects of Group \( F_{(2,14)} = 3.90, P = 0.05 \) and Electrode Site \( F_{(3,42)} = 7.44, P = 0.001 \) reached significance but the GroupxElectrode Site interaction did not
Fig. 1 Grand averages of the movement-related potentials preceding self-initiated movements for the normals (dark lines), and patients with positive schizophrenia (light lines) and negative schizophrenia (dotted lines).
Fig. 2 Grand averages of the movement-related potentials preceding externally triggered movements for the normals (dark lines), and patients with positive schizophrenia (light lines) and negative schizophrenia (dotted lines).
Fig. 3 Averaged movement-related potentials preceding self-initiated movements for one patient from the ‘positive’ group (thin dotted line) with high levels of medication (anticholinergic dose 100 mg, neuroleptic dose 320 mg) and one patient from the ‘negative’ group (thick solid line) with low levels of medication (anticholinergic dose 0 mg, neuroleptic dose 130 mg).
For the peak component the main effects of Group \[F(2, 12) = 5.20, P = 0.02\] and Electrode Site \[F(3, 42) = 7.95, P = 0.001\] reached significance but the Group\times Electrode Site interaction did not \((P > 0.05)\).

Pre-planned special contrasts revealed that the mean amplitudes of the MRPs prior to self-initiated movements for the late and the peak components were significantly lower in the patients with negative signs than in the normal controls \((P < 0.05)\), but there was no significant difference between the normal controls and the patients with positive signs \((P > 0.05)\). Post hoc \(t\)-tests revealed that the amplitude of the early and late components did not differ significantly between the two patient groups \((P > 0.05)\). Further investigation of the main effect of Electrode Site revealed that for the amplitude of the late component, the amplitude was most negative at FCz, CZ and C3. For the peak component the amplitude reached greatest negativity at FCz, CZ and FC3.

**MRPs prior to the externally triggered movements**

For the early, late and peak components there were no significant main effects of Group \((P > 0.05)\) and no significant Group\times Electrode Site interactions \((P > 0.05)\). There was a significant main effect of Electrode Site for the amplitude of the late \([F(4, 49) = 2.91, P = 0.04]\) and peak components \([F(4, 49) = 3.53, P = 0.01]\). Further post hoc examination of the Electrode Site effect revealed that for the late component the highest negativity was at Fz, FCz and FC3 while for the peak component the highest negativity was present at FCz, Fz and FC3.

**Slopes**

**MRPs prior to self-initiated movements**

For the self-initiated movements, for the slope of the early component, the main effect of Group \([F(2, 12) = 5.14, P = 0.02]\) was significant, but the main effect of Electrode Site and the Group\times Electrode Site interaction did not reach significance \((P > 0.05)\).

For the slope of the late component prior to the self-initiated movements, the main effects of Group \([F(2, 12) = 4.52, P = 0.03]\) and Electrode Site were significant \([F(3, 49) = 6.96, P = 0.01]\), but the Group\times Electrode Site interaction was not \((P > 0.05)\).

Pre-planned special contrasts revealed that prior to self-initiated movements the slopes of the early and late components were significantly reduced in the patients with negative signs compared to normals \((P < 0.02)\) and did not differ significantly between the patients with positive symptoms and the normals \((P > 0.50)\). Post hoc \(t\)-tests revealed that the slope of the early component was significantly reduced in the patients with negative signs compared to the patients with positive symptoms \((t = 3.2, d.f. = 8, P = 0.01)\) but the slope of the late component did not differ significantly between the two patient groups \((P > 0.1)\).

Further examination of the main effect of Electrode Site for slope of the late component revealed that the Electrode Sites of greatest negativity were FCz, FC3, and CZ.

**MRPs prior to externally triggered movements**

For the externally triggered movements, there were no significant main effects of Group or Electrode Site or their interaction for either the early or the late slope \((P > 0.10)\).

**Correlational analysis**

The amplitude of the early, late, and peak components and the slope of the early and late components of the MRP prior to self-initiated movements were correlated with clinical measures using Pearson’s correlation coefficients. For the patients with schizophrenia, no relationship was found between duration of illness and MRP amplitudes or slopes \((P > 0.05)\). There was a significant positive correlation between dose of anticholinergic medication and the amplitude of the late component at Pz \((r = 0.64, P = 0.04)\) and a significant negative correlation between dose of anticholinergic medication and the slope of the early component at Pz \((r = -0.62, P = 0.03)\) for the MRP prior to self-initiated movements. This means that higher doses of anticholinergic medication were associated with lower amplitude of the late BP, yet larger slope of the early BP at Pz. There was a significant negative correlation between dose of neuroleptic medication and the slope of the early component of the MRP prior to self-initiated movements at the three frontocentral sites (FC3, FCz, FC4) and at Pz \((r = -0.64 \text{ to } -0.78, P < 0.05)\). This means that higher doses of neuroleptic medication were associated with lower slopes of the early BP. There was a significant negative correlation between the rating of negative signs and the amplitude of the early component of the MRP at FCz \((r = -0.62, P = 0.04)\) prior to self-initiated movements. This means that patients with higher negative signs had lower early BP amplitude.

There was a significant positive correlation between the rating of positive symptoms and the amplitude of the late and peak components of MRPs prior to self-initiated movements at Fz and F4 \((r = 0.60 \text{ to } 0.67, P < 0.05)\). There was a significant positive correlation between the rating of positive symptoms and the slope of the early component at F3, Fz and FC3 \((r = 0.62 \text{ to } 0.77, P < 0.05)\) and slope of the late component at Fz, FC4, C3 and Cz \((r = 0.60 \text{ to } 0.62, P < 0.05)\) prior to self-initiated movements. These positive correlations signify that patients with higher ratings of positive symptoms have higher amplitudes and slopes (i.e. more normal) prior to self-initiated movements.
Discussion

The present results showed that prior to self-initiated movement relative to normals, the amplitude of the late and peak BP and the slope of the early and late BP were significantly lower for patients with predominance of negative signs but not patients with predominance of positive symptoms. Also, prior to self-initiated movement the slope of the early component was significantly lower for the patients with negative signs than patients with predominance of positive symptoms. The three groups did not differ significantly in MRP recorded prior to externally triggered movements. No significant differences were discovered between the normals and patients in the behavioural results (interresponse interval or reaction times). Although the EMGs among the groups appear different, this is unlikely to affect MRPs as it has been shown that BP are not affected by changes in the amplitude or velocity of finger movements (Dick et al. 1987). Thus, the differences seen in the MRPs cannot be attributed to differences in performance by the patients.

The current results concur with previous studies showing abnormal MRPs in schizophrenia (Timsit-Berthier et al. 1973; Chiarenza et al. 1985; Westphal et al. 1986; Singh et al. 1992; Karaman et al. 1997). However, the present results extend previous findings in two important respects. First, our results showed that the deficits in MRPs prior to self-initiated movements are particularly evident for patients with predominance of negative signs whereas the patients with predominance of positive symptoms did not differ significantly from normals. The amplitudes at some sites (e.g. FCz) do appear lower in the patients with positive symptoms compared to controls, but these differences were not large enough to reach statistical significance. Future studies with greater numbers of participants may clarify these differences. Second, our results demonstrated that differences from normal MRPs were present for patients with negative signs only prior to self-initiated movements requiring self-generated decision-making about the precise timing of movements as well as motor preparation but the patients did not differ from normals in terms of MRPs prior to externally triggered movements.

In contrast to the amplitudes which are based on measurements at a single point in time, the slopes of MRPs show changes in negativity over time and for this reason are perhaps more sensitive. In fact, the groups of patients with predominance of positive symptoms or negative signs only differed significantly in terms of the early slope, which is considered to reflect motor preparatory processes associated with supplementary motor area (SMA) activation (Deecke et al. 1969, 1976). This suggests that motor preparatory processes are more impaired in patients with schizophrenia and negative signs. As the two patient groups did not differ significantly in terms of the late slope, which according to Libet’s (1982) distinction coincides with the time course of volitional decision-making and intention to act, one inference would be that these processes are impaired in patients with schizophrenia regardless of the type of symptomatology.

Willed actions are purposeful, goal-directed behaviours. Three classes of decisions precede a voluntary action: ‘what to do’ – selecting an action among a set of possibilities, ‘how to do it’ – developing a strategy, and ‘when to do it’ – deciding the precise moment to begin (Kornhuber et al. 1989). The task used in this study required a volitional decision relating to ‘when to move’. Different criteria are relevant to defining an action as more or less volitional, for example intentionality, choice and control, attention and conscious awareness (Jahanshahi and Frith 1999). In a recent review of evidence, Jahanshahi and Frith (1999) provided support for a willed action system based on the frontostriatal circuits. More specifically, they suggested that: (1) intentional, self-generated actions (willed actions) are controlled differently from routine, stereotyped actions that are externally triggered by environmental stimuli, (2) willed actions are controlled by a network of frontal cortical (dorsolateral prefrontal cortex, supplementary motor area, anterior cingulate) and subcortical (thalamus and basal ganglia) areas, and (3) some of the deficits of patients with Parkinson’s disease or schizophrenia reflect impairment of willed actions.

In schizophrenia-impaired prefrontal activation during performance of tasks requiring volitional control (Weinberger et al. 1988; Andreasen et al. 1992; Seidman et al. 1994), reduced activation of the SMA (Schroeder et al. 1994) and an association between poverty of action and decreased rCBF in the dorsolateral prefrontal cortex and increased regional cerebral blood flow (rCBF) in the caudate (Liddle et al. 1992) have been reported. These suggest that the deficits in willed action in these patients may be mediated by dysfunction of the frontostriatal circuits. Using the same two types of movement as in the present study, in an investigation combining MRPs and measurements of rCBF with positron emission tomography (PET), we (Jahanshahi et al. 1995) have previously shown that patients with Parkinson’s disease tested off dopaminergic medication had a lower amplitude of the early and peak but not late BP prior to self-initiated movements than age-matched normals, the performance of which relative to a rest condition was associated with underactivation of the putamen, SMA, anterior cingulate, lateral premotor cortex and dorsolateral prefrontal cortex in these patients relative to normals. In contrast, for externally triggered movements, Parkinson’s patients and normals did not differ significantly either in terms of MRPs or rCBF.

Motivation is one of the variables shown to affect the BP (McAdam and Seales 1969). Although the deficits in MRPs in disorders such as Parkinson’s disease and schizophrenia are traditionally related to the motor symptoms of the former disorder such as akinesia and Bradykinesia and the less conspicuous motor abnormalities in schizophrenia such as clumsiness, disorganisation and slowness of movements (Manschreck 1986), it is also possible that motivational deficits such as apathy,
which can be a feature in both disorders and may also reflect frontostriatal dysfunction (Jahanshahi and Frith 1999), can also contribute to the deficits of MRPs observed in these disorders.

Studies in Parkinson’s disease (Dick et al. 1989; Jahanshahi et al. 1995) have shown that it is the amplitude of the early BP which is lower than normal in patients with Parkinson’s disease. In contrast, for patients with schizophrenia and negative signs both the early and late components are impaired relative to normals (Singh et al. 1992; present study). These results suggest that the different MRP components are differentially sensitive to different disorders such as Parkinson’s disease and schizophrenia in which impairment of frontostriatal circuits is implicated. The differential sensitivity of the MRP components is also supported by the fact that dopaminergic medication increases and anti-dopaminergic medication decreases the amplitude of the early BP only (Dick et al. 1987). In the present study we found that dose of neuroleptic medication had a significant negative correlation with the slope of the early MRP component prior to self-initiated movements, which suggests that those patients on higher levels of neuroleptic medication had reduced slopes for the early BP. The patients with predominance of negative signs were taking higher doses of neuroleptic medication than those with high positive symptoms, although the difference in dosage was not statistically significant. Nevertheless, given that anti-dopaminergic medication has been shown to reduce the amplitude of the early BP (Dick et al. 1987), it is possible that the significant reduction of the early slope in patients with high negative ratings relative to normals partly relates to their higher doses of neuroleptic medication. However, medication cannot be the only reason for reduction of MRPs in these patients as our sample of patients with positive symptoms who were also on neuroleptics did not differ significantly from normals in terms of MRPs. Also previous studies have reported reduced amplitude of the early and peak BP in both medicated and unmedicated patients with schizophrenia (Karaman et al. 1997). Animal studies have shown that cortical potentials are cholinergic dependent (Pirch et al. 1986). The two patient groups did not differ significantly in terms of dose of anticholinergic medication, but the patients with higher ratings of negative signs had higher levels of anticholinergic medication, which could possibly contribute to the reduced amplitudes of MRPs observed. But, as shown in Fig. 3, a patient with high ‘positive’ symptoms who was on the highest doses of anticholinergic and neuroleptic medication had larger amplitudes of MRPs prior to self-initiated movements relative to a patient with high ‘negative’ signs who was on a lower dose of medication. Nevertheless, the possible contributions of neuroleptic and anticholinergic medication to MRPs in schizophrenia need to be more systematically assessed in future studies.

This study showed that patients with higher ratings of negative signs had reduced MRPs prior to self-initiated movements but not externally triggered movements while the MRPs of the patients with higher ratings of positive symptoms were not impaired significantly for either type of movement. These findings support Frith’s (1992) hypothesis that patients with schizophrenia, particularly those with negative signs, are impaired in willed actions such as the self-initiated movement of the present study but are not impaired in stimulus-driven behaviour such as externally triggered movements assessed by us. The correlational analyses also confirmed that deficits in MRPs were associated with predominance of negative signs. Higher ratings of negative signs were associated with reduced amplitude of the early component at FCz prior to self-initiated movements, while higher ratings of positive symptoms were associated with higher MRP amplitudes and slopes (i.e. more normal) at frontocentral sites. Thus, the current results confirm that the distinction between positive symptoms and negative signs has heuristic value when investigating patients with schizophrenia.

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Reduced Negative Priming Does Indicate Reduced Cognitive Inhibition in Schizophrenia

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Introduction. Negative priming (NP) refers to the slowing of reaction times (RTs) that occurs when an ignored distractor in a first trial (prime) becomes the target in the subsequent trial (probe). Unlike normal controls, patients with schizophrenia fail to show significant NP. It has been proposed that delayed RTs in NP studies may be a result of perceptual mismatch rather than active inhibition, since the prime distractor and the probe target differ. The aim of this study was to examine spatial NP in schizophrenia using a new paradigm without perceptual mismatch.

Methods. Twelve patients with schizophrenia and 17 normals were tested on a spatial NP task. Prime distractors and probe targets matched in terms of colour and location or did not match.

Results. Normals showed significant spatial NP whether the probe target matched the prime distractor in terms of colour or not. In contrast, patients with schizophrenia did not show significant spatial NP.

Conclusions. In normals, NP can be observed even when prime and probe stimuli are identical while patients with schizophrenia fail to show NP in conditions with or without perceptual mismatch. This is the first unequivocal demonstration of impaired inhibitory processes in schizophrenia based on reduced NP effects.

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INTRODUCTION

There is considerable evidence that patients with schizophrenia have deficits in attentional processing. One feature of this is the greater distractibility of these patients in the presence of irrelevant information, for example as shown in dichotic shadowing tasks (Spring, 1985). Inadequate functioning of inhibitory attentional processes has been proposed as a mechanism of this increased distractibility in schizophrenia. The inability of patients with schizophrenia to maintain attentional set as demonstrated by the ‘cross over’ RT effect (Shakow, 1962), and the demonstration of abnormal recognition thresholds in a priming paradigm (Bullen and Hemsley, 1987) have all been considered evidence for ‘weakened inhibition’ in schizophrenia. Other empirical support for failure of inhibitory processes in schizophrenia exists. Inhibition of irrelevant information at an early stage of information processing has been termed ‘sensory gating’ (McDowd, Filion, Harris and Braff, 1993). One paradigm used to measure sensory gating is prepulse inhibition (PPI) which focuses on the eyeblink component of the startle reflex. Normally when the startle stimulus is preceded by a warning signal (prepulse), the eyeblink in the startle reflex is reduced, especially if the subject is told to attend to the prepulse (see McDowd et al., 1993 for a review). Patients with schizophrenia have reduced PPI (Braff, Grillon, and Geyer, 1992; Grillon, Ameli, Charney, Krystal, and Braff, 1992). Another paradigm that has been used to investigate inhibitory processes in schizophrenia is latent inhibition. A subject who is presented with a distracting stimulus such as bursts of white noise at the same time as a target stimulus takes longer to recognise the white noise as relevant in later trials. Subjects not pre-exposed to the white noise stimulus will identify it as relevant on subsequent trials much sooner. Studies with patients with schizophrenia have shown that although chronic medicated patients show similar latent inhibition as controls, unmedicated patients do not show latent inhibition (Baruch, Hemsley, & Gray, 1988). Such failures of inhibitory processes in schizophrenia have also been shown with other paradigms such as the Kamin blocking effect (Jones, Gray & Hemsley, 1992) and the antisaccade task (Fukushima, Fukushima, Miyasak, & Yamashita, 1994).

It has been suggested that some of the symptoms of schizophrenia, such as hallucinations, delusions and thought disorder may reflect a failure to limit the contents of consciousness due to a weakening of the inhibitory selective mechanisms involved in information processing, that allows intrusion of the output of preconscious processes into consciousness (Frith, 1979).

Another way to test inhibitory processes is by using the negative priming paradigm. First described by Tipper (1985) negative priming refers to the slowing of reaction times that occurs when an ignored distractor stimulus in a first trial becomes the target stimulus in the subsequent trial. Generally, in a negative priming experiment RTs are measured for response to two displays
presented in quick succession. The first display is called the prime, the second display is called the probe and both displays consist of a target and a distractor. There are two types of probes; ignored repetition and control. In the ignored repetition probe, the target is the same as the distractor of the prime. In the control probe, the target is different than the distractor in the prime. Negative priming is considered to have occurred if RT is slower in the ignored repetition condition than in the control condition. Later studies investigated spatial negative priming (Tipper, Brehaut, & Driver, 1990). In these, the delayed RTs occurred when the probe target shared the same location as the prime distractor (ignored repetition) compared to the control condition where the probe target was presented in a previously vacant location.

Normal control subjects show delayed reaction times in the ignored repetition condition presumably because the active task of ignoring the stimulus in the first trial is carried over into the second trial and inhibits the subject’s response to this previously ignored stimulus (Tipper and Cranston, 1985; Tipper, Weaver, & Kirkpatrick, 1991). Patients with schizophrenia do not show a significantly increased RT when a previously ignored stimulus becomes the target (Park, Lenzenweger, Puschel, & Holzman, 1996; Williams, 1996; Beech, Powell, & McWilliam, 1989; Laplante, Everett, & Thomas, 1992; David, 1995; Salo, Robertson, & Nordahl, 1996), in line with the proposal of a breakdown of inhibitory processes (Frith, 1979).

The most widely accepted view of negative priming is that it represents the operation of inhibitory mechanisms in selective attention such that the distracting stimuli are selectively inhibited during the prime trials (e.g. Tipper, 1985). There have been other accounts besides this selective inhibition to explain the phenomenon of negative priming. According to the ‘episodic retrieval’ account the ignored distractor in the prime ‘episode’ is encoded with a ‘to-be-ignored’ tag and as a result responses to previously ignored probes are slowed by the automatic retrieval of the prior episode along with the to-be-ignored tag (Neill and Valdes, 1992). Recently Milliken, Joordens, Merikle and Seiffert (1998) have suggested a ‘temporal discrimination’ account of negative priming. They propose that slowed RTs results from ambiguity in the categorisation of the probe stimulus as ‘old’ or ‘new’ relative to the prime. On ignored repetition trials, the familiarity of the probe target which has been previously seen as the ignored distractor on the prime trial, rules out its classification as ‘new’ and yet is insufficient to allow its consideration as ‘old’. This ambiguity in the temporal discrimination process is considered to underlie the delayed RTs on ignored repetition trials.

From a different perspective, Park and Kanwisher (1994) have suggested the interpretation of previous spatial negative priming studies as reflecting the operation of inhibitory processes may actually be a result of perceptual mismatch rather than indicative of active inhibition. Because the probe target differs from the prime distractor in some way, either in colour, identity or size,
the hesitation and hence prolonged RT shown by normals in responding on the probe trial may have nothing to do with reduced inhibition but instead reflect the detection of the perceptual mismatch. This point has been addressed by Milliken, Tipper, & Weaver (1994), Tipper, Weaver, & Milliken (1995) and Watson and Tipper (1997). Milliken et al (1994) confirmed that perceptual mismatch can contribute to negative priming in some situations. In a series of three experiments Tipper et al (1995) found a spatial negative priming effect in normals whether the prime distractor and target probe matched or mismatched in terms of size or identity. However, the spatial negative priming effect was smaller when the colour of the prime distractor and target probe matched, than when they mismatched. Therefore, Tipper et al (1995) concluded that perceptual mismatch and distractor inhibition produce additive effects on RT. In a subsequent study Watson and Tipper (1997) found reduced negative priming in schizotypal subjects using a negative priming paradigm on which there was no perceptual mismatch.

The majority of the previous studies which have examined negative priming in patients with schizophrenia used Stroop stimuli in which the stimuli have a colour mismatch confound, because the prime distractor and the probe target were different colours (Beech et al., 1989; Laplante et al., 1992; David, 1995; Salo et al., 1996; Salo, Robertson, Nordahl, & Kraft, 1997). The two studies that examined spatial negative priming in schizophrenia (Park et al., 1996; McDowd et al., 1993) with a task other than the Stroop used an X-O paradigm which also involves an identity mismatch between the prime distractor and probe target. This means that reduced negative priming in schizophrenia in these studies cannot unequivocally be attributed to a failure of inhibition and instead may indicate these patients’ insensitivity to the effects of perceptual mismatch between stimuli due to poor episodic encoding or retrieval for prime/probe comparisons relative to normal subjects. Although inhibitory deficits have been demonstrated clearly from other paradigms, studies using negative priming tasks lead to ambiguous interpretations, which are not clearly attributable to reduced inhibitory effects. The aim of this study is to examine the spatial negative priming effect in schizophrenia using a new paradigm that allows the effects of perceptual mismatch on RT to be considered independently of any spatial negative priming effects. We predicted that patients with schizophrenia would show significantly less negative priming, both in conditions where the prime distractor and probe target matched or had a perceptual mismatch.

METHOD

Subjects

Table 1 lists the characteristics of the subject groups. Fourteen patients with schizophrenia and 17 normals (3 female, 14 male) took part in the study. Two patients had RTs which were extreme compared to group means, one patient on
TABLE 1  
Characteristics of subjects.

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Patients with Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 14, Female 3</td>
<td>Male 10, Female 2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.5 (8.2)</td>
<td>41.3 (6.5)</td>
</tr>
<tr>
<td>Beck Depression</td>
<td>6.4 (6.5)</td>
<td>15.0 (8.0)</td>
</tr>
<tr>
<td>Inventory (0-63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS (0-175)</td>
<td></td>
<td>6.1 (8.0)</td>
</tr>
<tr>
<td>SANS (0-120)</td>
<td></td>
<td>18.9 (12.0)</td>
</tr>
<tr>
<td>Dose of anticholinergic (Disipal equivalent)</td>
<td>37.5 (71.1) (range 0-200 mg)</td>
<td></td>
</tr>
<tr>
<td>Dose of neuroleptic (chlorpromazine equivalent)</td>
<td>377.1 (305.9) (range 0-825 mg)</td>
<td></td>
</tr>
</tbody>
</table>

All values given are means, standard deviations in brackets. SAPS = The standardised assessment for positive symptoms. SANS = The standardised assessment for negative symptoms (Andreasen, 1984)

2 of the 4 and one patient on all 4 measures of interest (C+, C−, L+, L−). These two cases were therefore excluded. The remaining patients (2 female, 10 male) and normals did not differ in terms of male to female ratio ($x^2 = 0.11$, df = 1, $P = .74$), age ($t = 1.30$, df = 27, $P = .20$) handness, ($t = 1.56$, df = 27, $P = .13$) or estimates of ‘premorbid’ verbal IQ obtained from the National Adult Reading Test (NART, Nelson and Willison, 1991) ($t = 1.45$, df = 22, $P = .16$). The two groups did differ in terms of scores on the Beck Depression Inventory (BDI, Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) with the patients having higher scores than the normals ($t = 2.38$, df = 25, $P = .03$). NART Verbal IQ scores for five controls and BDI scores for two controls were missing. The patients with schizophrenia were rated on the Scale for Assessment of Positive Symptoms and the Scale for Assessment of Negative Signs (Andreasen, 1984) and as a group had higher ratings of negative signs than positive symptoms ($t = 5.23$, df = 12, $P < .001$).

Task

The task was the same as that in experiment 3 of Tipper et al. (1995). Figure 1 presents the prime and probe conditions. The subject initiated each trial by pressing the start key that was located under the index finger on the joystick. After pressing the start key four empty boxes appeared which indicated the possible stimulus locations, above, below, to the left and right of fixation. After
a delay of 1000 ms the prime display appeared, which were 2 Xs of different colours that appeared in two randomly chosen boxes, and a small coloured square presented at fixation simultaneously with the 2 Xs (in Tipper et al.’s (1995) experiment 3 the coloured square appeared 57 ms after the onset of Xs and remained on the screen for 29 ms). One X was the same colour as the small central square. Subjects were instructed to move the joystick in the direction of the target X, the colour of which matched the central coloured square which acted as the colour selection cue. Both speed and accuracy were emphasised. The prime remained on the screen until the subject responded. Auditory feedback was given in the form of an error tone for an incorrect response and a 50 ms click for a correct response.

The response stimulus interval (RSI) was 500 ms and only the four boxes were visible during this interval. The probe colour selection cue appeared after the 500 ms RSI and at the same time two coloured Xs were presented. As for the prime, the subjects were required to move the joystick in the direction of the X
that matched the central coloured square which acted as the colour selection cue. Both speed and accuracy were emphasised. As for the prime, the display remained on the screen until the response was made, and auditory feedback was provided on each trial. After the auditory feedback following the response to the probe a written prompt appeared on the screen instructing the participant to press the start key to continue.

**Design**

The study had a mixed between-groups and within-subjects design. The between groups factor was Groups (schizophrenia vs normals). There were 2 repeated measures within subject variables, Location and Colour. There were two levels of Location: L+ and L−. In L+ condition, the probe target appeared in the same location as the prime distractor; and in the L−condition, the probe target appeared in a box that differed from the location of the prime distractor and was vacant during the prime. In all conditions, the probe distractor appeared in a previously vacant box. The two levels of Colour were C+ and C−. In C+ condition, the probe target was the same colour as the prime distractor; in C−condition, the probe target was in a different colour than the prime target or distractor. In all conditions, the probe distractor appeared in a colour that was not used for the prime. Therefore there were four conditions: C−L− (colour mismatch, different location—control), C−L+ (colour mismatch same location—ignored repetition), C+L− (colour match, different location—control), C+L+ (colour match, same location—ignored repetition). There were 4 possible locations; above, below, to the left and right of the central square and there were also 4 possible colours: blue, green, yellow, and purple, selected to be easily discriminable.

Each condition started with a practice block (Block 0) followed by a test block (Block 1). The number of trials for the two types of block in each of the 4 conditions is listed below.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Block 0</th>
<th>Block 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>C−L−</td>
<td>12</td>
<td>96</td>
</tr>
<tr>
<td>C−L+</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>C+L−</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>C+L+</td>
<td>3</td>
<td>24</td>
</tr>
</tbody>
</table>

These proportions were used to ensure that subjects could not use properties of the prime distractor to predict the colour or location of the probe target. Stimulus presentation and RTs were measured to the nearest ms. Millisecond timing of displays and responses was achieved using the TIMEX function (Bovens and Brysbaert, 1990). The data of importance were the median RTs for correct responses and error percentages. Prime and probe RTs were used only if the responses to both prime and probe were correct. Responses greater than 3000 ms
were counted as errors. The four conditions were randomised in terms of order of presentation. All 243 trials were presented in one session, with a 30 second break after every 50 trials. The first 27 trials were practice and not included in the analysis. The entire session lasted approximately 30 minutes.

RESULTS

Prime Displays

A one way Analysis of Variance (ANOVA) were used to examine the RT for the prime condition. RTs for the patients with schizophrenia were significantly slower than those for the normals \[F(1,27)=21.92, P<.01\]. A one way ANOVA was carried out on the percentage of errors in the prime condition. The patients with schizophrenia and the normals did not differ in terms of percent of errors made \[F(1,27)=0.23, P>.05\].

Probe Display

A 3 way ANOVA was carried out. The between subjects factor was Group (schizophrenia vs normals) and the within subject variables were Colour (C+ vs C-) [colour match or colour mismatch] and Location (L+ vs L-) [ignored repetition or control]. The mean median RTs for each condition in each group are shown in Figure 2.

The main effect of Colour was not significant \[F(1,27)=0.19, P>.05\]. The main effect of Group was significant \[F(1,27)=19.22, P<.01\] due to slower RTs for the patients (725 ms, SD=108) than for the normal controls (566 ms, SD=87). The main effect of Location \[F(1,27)=31.12, P<.01\] was also significant as RTs were slower for the ignored repetition conditions (L+) (641 ms, SD=121) than for the control conditions (L-) (623 ms, SD=127). There was no significant Colour \times Location interaction, nor did Group show a significant interaction with either of the other two variables \((P>.05)\). The three way Group \times Colour \times Location interaction was also nonsignificant \((P>.05)\).

Given our interest in negative priming effects (control conditions compared to ignored repetition conditions) a series of post hoc tests were carried out. In normals, the comparison of C+L− and C+L+ was significant \((t=3.9, df=16, P<.01)\). T-tests revealed that the normals also had significantly slower RTs in the C−L+ than in the C−L− condition \((t=4.7, df=16, P<.001)\). Thus the normal controls exhibited significant spatial negative priming in both the colour match and colour mismatch conditions.

However, these same comparisons for the patients with schizophrenia were not significant. The RTs for the patients with schizophrenia did not differ significantly between the C+L+ condition and the C+L− condition \((P>.05)\) (colour match) or between the C−L+ condition and the C−L− condition \((P>.05)\) (colour mismatch). Therefore the patients with schizophrenia failed to show
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FIG. 2. The mean of median reaction times (RT) to the probes for the patients with schizophrenia and normal controls in each of the four conditions C-L-control, colour mismatch; C-L+ ignored repetition, colour mismatch; C+L-control, colour match; C+L+ ignored repetition, colour match. Spatial negative priming indicated by slower RTs for ignored repetition (L+, white bars) than control (L-, black bars) conditions for the normals. *Significance P < .05.

significant spatial negative priming in either the colour match or the colour mismatch condition.

Probe Error Data

The mean percentage of errors for each group in each condition are presented in Table 2. A 3 way repeated measures ANOVA was carried out on the error percentages. The between subjects factor was Group (patients with schizophrenia vs normals) and the within subject variables were Colour (C+ vs C−) and Location (L+ vs L−). There were no significant main effects of Group, Colour, or Location (P > .05) and there were no significant interactions (P > .05).

Correlational Analysis

To determine the extent of the spatial negative priming effect the RTs for the ignored repetition conditions were subtracted from the RTs for their respective control conditions: [(C−L−)−(C−L+)] for the colour mismatch condition, and [(C+L−)−(C+L+)] for the colour match condition. These measures of spatial negative priming effect were then correlated with clinical measures using
TABLE 2
Mean Percentage of Errors (and standard deviations) For Each Group in Each Condition

<table>
<thead>
<tr>
<th>Normal Location</th>
<th>Patient Location</th>
<th>Normal Errors</th>
<th>Patient Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-L-</td>
<td>C-L+</td>
<td>1.40 (1.47)</td>
<td>2.33 (2.51)</td>
</tr>
<tr>
<td>C-L+</td>
<td>C-L-</td>
<td>1.11 (1.31)</td>
<td>2.79 (2.86)</td>
</tr>
<tr>
<td>C+L-</td>
<td>C+L+</td>
<td>1.98 (1.74)</td>
<td>1.58 (2.03)</td>
</tr>
<tr>
<td>C+L+</td>
<td>C+L-</td>
<td>1.47 (2.91)</td>
<td>2.78 (4.10)</td>
</tr>
</tbody>
</table>

C+L+: the probe target was the same colour and appeared in the same location as the prime distractor; C+L-: the probe target was the same colour but appeared in a different location to the prime distractor; C-L+: the probe target was a different colour but in the same location as the prime distractor; C-L-: the probe target was a different colour and was in a different location than the prime distractor.

Pearson's correlation coefficients. There was a significant positive correlation between scores on the SAPS (Andreasen, 1984) and the magnitude of the spatial negative priming effect in the colour match condition, that is the [(C+L-)-(C+L+)] difference score \((r=.59, P=.04)\). This means that patients with higher ratings of positive symptoms showed less negative priming.

DISCUSSION

In summary, the significant main effect of location signified occurrence of significant spatial negative priming. The main effect of colour was not significant indicating that colour match or mismatch did not affect RTs. The groups differed significantly reflecting slower RTs for the patients with schizophrenia than for the normal controls. There were no significant group interactions but post-hoc comparisons revealed that the normals showed significant spatial negative priming effects both in the colour match and in the colour mismatch conditions, while the patients with schizophrenia failed to exhibit significant levels of negative priming effects in either condition.

It has been proposed that the increased RT previously attributed to spatial negative priming effects may be due to perceptual mismatch since the prime distractor differed from the probe target in terms of either colour, identity, or size (Park and Kanwisher, 1994). The current results add support to the findings of Milliken et al. (1994) and Tipper et al. (1995) that in normal subjects spatial negative priming effects are present even when other stimulus features such as colour, identity and size are held constant between the prime distractor and the probe target. In the present study there was no significant difference in the degree of spatial negative priming effects between the colour match and the colour mismatch condition.

Recently, Tipper (1998) has noted that the accounts of negative priming in terms of inhibition of the internal representation of a distractor in the process of selective attention or detection of perceptual mismatch in the process of episodic
retrieval which have respectively been described as forward acting and backward acting processes are not necessarily antagonistic or mutually exclusive. Instead, Tipper suggests that as both encoding and retrieval processes are implicated in the negative priming phenomenon, the inhibition account which emphasises the encoding process acting on the prime display and the episodic account which focuses on the properties of the probe that enable retrieval of the prime encoding episode are both relevant to a fuller understanding of negative priming effects. In this respect, both accounts are relevant to appreciation of reduced negative priming in schizophrenia as these patients also show deficits in episodic encoding and retrieval (Brebion, Amador, Smith, & Gorman, 1997; Andreasen, 1997) as well as inhibitory processes (see Introduction).

Evidence implicates dopamine as a neurotransmitter with a role in mediating negative priming. However the precise direction and nature of this role is unclear. David (1995) has noted that in the more acute phase, when positive symptoms predominate, reduced negative priming in schizophrenia has been attributed to a hyper-dopaminergic state. However, several lines of evidence oppose such a view. First, there is evidence from normal subjects showing that neuroleptics, that is dopamine antagonists, increase negative priming (Beech, Powell, McWilliam & Claridge, 1990). Second, reduced negative priming has been reported in patients with schizophrenia who were (Beech et al., 1989; Laplante et al., 1992) or were not (Salo et al., 1996) tested while taking neuroleptic medication. For example, Salo et al. (1996) tested 12 patients with schizophrenia withdrawn from neuroleptic medication and found no evidence of negative priming. In contrast, David (1995) found that in a small group of neuroleptic free patients with schizophrenia or affective disorder there was some suggestion that negative priming was present. Third, patients with Parkinsons’ disease, a hypo-dopaminergic disorder, fail to show negative priming (Downes, Sharp, & Sagar, 1991). In reviewing the effects of neuroleptics on cognitive function, Spohn & Strauss (1989) concluded that neuroleptics tend to normalize the performance of patients with schizophrenia and reduce distractibility on attentional tasks. This is clearly not the case for negative priming effects. In the present study, all patients were on neuroleptic medication and none showed any substantial degree of negative priming as observed in the normal controls. Also, the dose of neuroleptics did not show any significant associations with any of the measures of negative priming. Therefore, available information about the contribution of dopamine overstimulation or understimulation to negative priming is inconsistent. Future studies need to evaluate this question more systematically by examining negative priming in early newly diagnosed patients prior to the introduction of neuroleptic medication, chronic treatment with which may in itself alter dopaminergic transmission.

Because of the post hoc nature of the group differences, it could be argued that the present results constitute relatively weak demonstration of reduced
negative priming in patients with schizophrenia. Future studies should include a larger number of participants and patients with higher ratings of symptoms. Reduced negative priming has been demonstrated for patients with schizophrenia and predominance of positive or negative symptoms, with some studies suggesting that the abnormality of negative priming is greater in those with relatively higher ratings of negative symptoms (Laplante et al., 1992), while others reported reduced negative priming in patients with positive symptoms (Park et al., 1996; Williams, 1996). The latter study reported reduced negative priming in subgroups of patients with reality distortion and disorganisation. Park et al. (1996) found reduced negative priming in acute but not chronic patients with schizophrenia. In the present study, we did not have a sufficient number of patients with predominance of positive symptoms vs negative signs to compare negative priming across the subgroups. However, the correlational analysis suggests that higher ratings of positive symptoms were associated with less negative priming in the colour match condition. This finding suggests weakened inhibition may contribute to positive symptoms in schizophrenia.

Lavie and colleagues (Lavie & Tsai, 1994; Lavie & Fox, 1998) have suggested that high perceptual load in processing of relevant information is a necessary condition for early selection to occur. In normals, evidence has been provided to show that with higher perceptual load, distractor interference is reduced. In relation to negative priming, these authors have shown that manipulating the perceptual load of relevant processing by increasing the set size of the target reduced the amount of negative priming associated with processing of a distractor stimulus (Lavie & Fox, 1998). Reduced negative priming in schizophrenia can be incorporated into this view of the relevance of perceptual load to negative priming. It can be suggested that because of capacity limitations (Granholm, Asarnow, & Marder, 1996), perceptual load is higher in schizophrenia than normals across all tasks, so that less or no space capacity is available to allocate to inhibition of irrelevant/distractor stimuli.

It is possible that in negative priming paradigms selective inhibition of the distractor does in fact occur in schizophrenia but it decays more rapidly compared to normal subjects, such that at the time of the probe trial it produces a less detrimental effect on the subsequent act of selection. As an alternative to this ‘rapid dissipation of inhibition’, it is possible that the ‘strength’ of the initial inhibition is somewhat weaker so that it does not build up rapidly or sufficiently enough to carry over into the subsequent act of selection. In future studies, it should be possible to differentiate between these two alternative explanations of reduced negative priming in schizophrenia: rapidly decaying inhibition vs weakened and delayed build up of inhibition. The interval between trial n and n-1 is important in negative priming tasks and Laplante et al. (1992) have shown that the interval between prime and probe trials affects the degree of negative priming observed in patients with predominance of positive or negative symptoms of schizophrenia. In future studies, supplementing behavioura
investigation of the negative priming effect with recording of event-related
cortical potentials which have high temporal resolution and provide ms by ms
data will be valuable in providing information about the time course of operation
of inhibitory processes between the prime distractor and probe target.

In summary, in normal subjects negative priming was found even when there
was no perceptual mismatch between the ignored prime distractor and the target
probe, adding support to the findings of Milliken et al. (1994) and Tipper et al.
(1995). Post hoc analysis showed reduced negative priming in patients with
schizophrenia in conditions with or without perceptual mismatch. This is the
first clear and unequivocal demonstration of reduced inhibition in schizophrenia
based on reduced negative priming effects.

REFERENCES


