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Frontal–striatal cognitive deficits in patients with chronic schizophrenia

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Summary

Spatial working memory and planning abilities were assessed in 36 hospitalized patients with chronic schizophrenia, using the computerized Cambridge Neuropsychological Test Automated Battery (CANTAB), and compared with those of normal subjects and patients with neurological disorders (frontal lobe lesions; temporal lobe and amygdalo-hippocampal lesions; Parkinson's disease), matched for age, sex and National Adult Reading Test IQ. The patients in the group with temporal lobe lesions were unimpaired in their performance on these tasks. Patients with schizophrenia were impaired on visuo-spatial memory span compared with all the other groups, while severity of Parkinson's disease was correlated with the degree of impairment on this task. The patients with schizophrenia and those with frontal lobe lesions were impaired on a 'spatial working memory' task, with increased 'between-search errors'. Patients with Parkinson's disease performed this task poorly compared with the younger control subjects. Patients with schizophrenia were unable to develop a systematic strategy to complete this task, relying instead on a limited visuo-spatial memory span. Higher level planning ability was investigated using the CANTAB 'Tower of London'. All groups were equally able to complete the task. However, the groups of patients with schizophrenia and frontal lobe lesions made fewer perfect solutions and required more moves for completion. Movement times were significantly slower in the schizophrenia group, suggesting impairment in the sensorimotor requirements of the task. The patients with schizophrenia were not impaired in their 'initial thinking' (planning) latencies, but had significantly prolonged 'subsequent thinking' (execution) latencies. This pattern resembled that of the group with frontal lobe lesions and contrasted with the prolonged 'initial thinking' time seen in Parkinson's disease. The results of this study are indicative of an overall deficit of executive functioning in schizophrenia, even greater than that seen in patients with frontal lobe lesions. However, the pattern of results in schizophrenia resembled that seen in patients with lesions of the frontal lobe or with basal ganglia dysfunction, providing support for the notion of a disturbance of frontostriatal circuits in schizophrenia. Our findings also indicate that there is a loss of the normal relationships between different domains of executive function in schizophrenia, with implications for impaired functional connectivity between different regions of the neocortex.

Keywords: working memory; planning; bradyphrenia; frontal–subcortical connections; functional connectivity

Abbreviations: CANTAB = Cambridge Neuropsychological Test Automated Battery; NART = National Adult Reading Test; SPECT = single photon emission computerized tomography; WAIS = Wechsler Adult Intelligence Scale

Introduction

The neural substrates of schizophrenia remain unclear, although advances in neuroimaging and post-mortem analyses have implicated a range of candidate structures and neurotransmitter systems in the pathogenesis of the disorder. These include the temporal and frontal cortices, hippocampus, amygdala, striatum and thalamus, as well as dopaminergic,

serotoninergic and glutamatergic systems (for reviews, *see*: Falkai and Bogerts, 1995; Owen and Simpson, 1995; Bilder and Szeszko, 1996; Woodruff and Lewis, 1996). Recently, there has been particular interest in the possible contribution of the frontal cortex and its interactions with other structures, notably the hippocampus and basal ganglia. Hypotheses have been advanced which seek to explain the symptomatology of schizophrenia in terms of the cognitive processes subserved by these structures (Robbins, 1990, 1991; Buchsbaum, 1990; Goldman-Rakic, 1990; Weinberger, 1991; Pantelis *et al*., 1992).

Neuropsychological studies of patients with schizophrenia have consistently identified deficits of executive function, traditionally considered sensitive to frontal lobe damage, with deficits apparent on tasks such as the Wisconsin Card Sorting Test, verbal fluency, the Stroop task and the 'Tower of London' (Kolb and Whishaw, 1983; Taylor and Abrams, 1984, 1987; Weinberger *et al*., 1986; Goldberg *et al*., 1990, 1993; Morice, 1990; Liddle and Morris, 1991; Shallice *et al*., 1991; Morrison-Stewart *et al*., 1992; Morris *et al*., 1995). These findings have been supported by the results of functional neuroimaging studies suggesting 'hypofrontality' in schizophrenia. The latter has been most consistently demonstrated using cognitive activation paradigms (Weinberger *et al*., 1986; Berman *et al*., 1988; Andreasen *et al*., 1992; Buchsbaum *et al*., 1992; for review, *see* Velakoulis and Pantelis, 1996).

Although abnormal function has been demonstrated in the prefrontal cortex, there is scant evidence of anatomical pathology of this brain area (Shelton *et al*., 1988; Andreasen *et al*., 1990). Recent investigators have attempted to explain the apparent hypofrontality by examining distant sites, such as hippocampus and basal ganglia, and the pathways which connect them with the prefrontal cortex (Robbins, 1990, 1991; Weinberger, 1991; Pantelis *et al*., 1992). In particular, it has been proposed that pathology in the hippocampus explains the hypofrontality observed in functional imaging studies, especially those involving the dorsolateral prefrontal cortex (Weinberger, 1991; Weinberger *et al*., 1992). This hypothesis receives support from the findings of neuropathological and structural neuroimaging studies (Bogerts *et al*., 1985, 1990; Brown *et al*., 1986; Suddath *et al*., 1989, 1990). Primate studies also suggest that the hippocampus and its connections with the dorsolateral prefrontal cortex plays an important role in executive function and these models have been applied to schizophrenia (Goldman-Rakic, 1990). However, to date, few human studies have examined the role of the hippocampi or other medial temporal lobe structures in executive function and the results of those studies have been contradictory (Frisk and Milner, 1990; Corcoran and Upton, 1993; Owen *et al*., 1996*c*).

While structural changes in the hippocampus may provide one explanation for the hypofrontality observed in schizophrenia, other investigators have suggested that it is the connections between prefrontal cortical areas and the basal ganglia and thalami which are important. Support for this hypothesis includes PET studies of drug-naive patients with schizophrenia, which have identified reduced metabolism in basal ganglia structures while confirming hypofrontality (Buchsbaum *et al*., 1992; Siegel *et al*., 1993), while in another study of never-medicated patients changes were identified in the globus pallidus (Early *et al*., 1987). Other studies have identified changes in both medial temporal lobe structures as well as changes in the striatum (Friston *et al*., 1992). Such investigations suggest that, while dysfunction of frontal–hippocampal circuits may provide an explanation of hypofrontality in schizophrenia, another possible contribution to the cognitive deficits in schizophrenia is made by dysfunction of frontal–striatal–thalamic circuitry (Frith and Done, 1988; Robbins, 1990, 1991; Buchsbaum *et al*., 1992; Siegel *et al*., 1993; Pantelis and Brewer, 1995, 1996), possibly reflecting disturbed pathophysiology in subcortical areas, such as the basal ganglia or thalami (Barnes, 1988; Pantelis *et al*., 1992; Collinson *et al*., 1996).

The frontal–striatal–thalamic pathways are highly organized with parallel, segregated circuits throughout their course (Alexander *et al*., 1986; DeLong *et al*., 1990). These subserve motor and ocular motor function via loops involving the supplementary motor area and the frontal eye fields, and are involved in cognitive function, emotion and behaviour via functional loops separately involving dorsolateral prefrontal cortex, orbitofrontal and anterior cingulate regions of the prefrontal cortex. Dysfunction of these prefrontal regions and their associated circuits has been implicated as important in understanding the range of symptoms, disturbances of behaviour and neuropsychological deficits evident in schizophrenia (Robbins, 1990, 1991; Pantelis and Brewer, 1995, 1996). In contrast, the frontal–hippocampal hypothesis implicates the dorsolateral prefrontal cortex specifically, which may only explain a limited range of the observed deficits in this disorder.

While these hypotheses provide two possible explanations for the observed hypofrontality in schizophrenia, only a few recent studies have made direct neuropsychological comparisons between patients with schizophrenia and those with disorders affecting the neocortex or subcortical structures (Gold *et al*., 1994; Heaton *et al*., 1994; Hanes *et al*., 1996*a*, *b*). The main aim of the present study was to characterize the neuropsychological profile of patients with chronic schizophrenia on a test battery [the Cambridge Neuropsychological Test Automated Battery (CANTAB)] that has been shown to be sensitive to impairments of set shifting, working memory and planning, not only in neurosurgical cases of frontal or temporal lobe injury (including amygdalo-hippocampectomy) (Owen *et al*., 1990, 1991, 1995, 1996*c*), but also in disorders of the basal ganglia, including Parkinson's disease (Morris *et al*., 1988; Sahakian *et al*., 1988; Downes *et al*., 1989; Owen *et al*., 1992, 1993*a*, *b*; Robbins *et al*., 1992, 1994*a*). The test battery includes a form of the 'Tower of London' test of planning (Shallice, 1982) which incorporates measures of thinking latency as well as accuracy and a test of self-ordered spatial working

memory based on analogous tasks used in experimental animals (Passingham, 1985; Petrides, 1995). The latter test yields measures of performance on spatial working memory, and the optimal strategy used to complete the task, which is presumed to be an indicator of executive function. While studies to date have identified deficits of spatial short-term memory in schizophrenia (e.g. Park and Holzman, 1992), no previous study has examined the various components of working memory in schizophrenia assessed by this task.

Therefore, in order to examine the nature and extent of the deficits in executive function in schizophrenia, patients with this illness were compared with matched control subjects and matched groups of patients with neocortical damage, involving frontal lobe or medial temporal lobe structures, or Parkinson's disease. This allowed examination of the key question arising from the two hypotheses of hypofrontality outlined above, specifically, whether the pattern of neuropsychological deficits in schizophrenia more closely resembles that resulting from frontal–striatal dysfunction or the performance observed in patients with lesions in medial temporal lobe structures.

Methods

Patients and control subjects

Patients with schizophrenia

All in-patients between 18 and 65 years of age who were resident in a long-stay psychiatric hospital (Horton Hospital, Epsom, UK) for >1 year, with a diagnosis of schizophrenia, were screened for inclusion in the study. Patients fulfilling DSM-III-R (American Psychiatric Association, 1987) criteria for schizophrenia and who could not be excluded for other reasons, outlined below, were asked to participate. In-patients from Horton Hospital originated from the North-East Thames region of London, though many who had been in-patients for more than a few years originated from across the country. Of 111 patients meeting these criteria, 51 patients were excluded for the following reasons: four were acutely disturbed; one was unable to work the computer due to severe tremor; one had a history of recent drug abuse as assessed with urine drug screening; 11 patients had poor eyesight; five were leucotomized; four had a history of significant head injury, cerebral vascular accident or evidence of dementia; four with history of epilepsy; four had a history of thyroid disease or were being treated with thyroxine; one patient with schizophrenia and Wilson's disease was excluded; 14 refused to participate in the study and one patient became deluded about the computer and could not be tested; one patient relapsed during testing.

While the CANTAB was administered to the remaining 60 patients with chronic schizophrenia, the current study reports findings from those 36 patients who could be appropriately matched to the other patient groups, according to age, sex and the National Adult Reading Test IQ (NART IQ) (Nelson, 1982). Two separate comparisons were undertaken for this group of patients with schizophrenia: (i) Comparison 1, which compared patients with schizophrenia with age-matched normal control subjects, and with groups of patients with frontal or temporal lobe lesions; (ii) Comparison 2, which compared patients with schizophrenia with Parkinson's disease patients and their respective (older) age-matched normal control subjects. All patients and control subjects provided informed consent to participate in the study, which was approved by the Riverside Ethics Committee (London, UK).

Comparison 1: schizophrenia versus frontal and temporal lobe lesions

Patients with schizophrenia. The 36 patients with schizophrenia who undertook the 'working memory and planning' test battery, were chosen to match the other neurological groups and normal control subjects as closely as possible with regard to age, sex and NART IQ (*see* Table 1). The patients and control subjects did not differ significantly with respect to sex ($\chi^2 = 5.59$) and were well matched for NART IQ [$F(3,115) = 1.215$]. However, the temporal/amygdalo-hippocampectomy group were significantly younger than the other groups [$F(3,118) = 9.965$, $P < 0.0001$]. For the analyses that follow, age was used as a covariate where appropriate.

The 36 schizophrenic patients (29 male, seven female) had a mean age (± SEM, standard error of the mean) of 48.31 ± 1.70 years, mean age at onset of illness was 20.69 ± 1.06 years, mean length of illness was 27.61 ± 1.64 years, mean length of current admission was 19.17 ± 2.13 years, mean total length of all admissions was 23.33 ± 1.87 years, and mean daily dose (± SEM) of neuroleptic medication, expressed as milligram equivalents of chlorpromazine was 1401.1 ± 218.6 mg. The mean NART IQ (± SEM) was 97.2 ± 1.5). These patients were therefore a chronic population who had been hospitalized for most of their illness.

Normal control subjects. Data from normal control subjects who had completed the CANTAB tests were available from studies conducted by the Cambridge group and were mainly drawn from the North-East Age Research panel in Newcastle-upon-Tyne. These normal control subjects were similar to those used in previous studies of the CANTAB (e.g. Owen *et al*., 1990).

Patients with frontal lobe lesions. Data from patients with frontal lobe lesions who had undergone unilateral or bilateral frontal lobe surgery were derived from the sample described by Owen *et al*. (1990). Three patients with frontal lobe lesions who had CT scan evidence of subcortical damage were excluded. Of the 26 patients with frontal lobe lesions in this study, 15 had right sided frontal lobe excisions (three with right frontal lobectomy, three cases had an anterior

Table 1 *Characteristics of patients and control subjects for Comparisons 1 and 2*

	Main groups		Comparison 1		Comparison 2	
	Schizophrenia patients (n = 36)	Matched control subjects (n = 31)	Frontal lobe lesions (n = 26)	Temporal lobe/ amygdalo-hippo-campal lesions (n = 29)	Parkinson's disease (medicated) (n = 29)	Older control subjects (n = 29)
Mean age in years	48.31	47.48	41.73	32.72*	62.24	66.41
± SEM	± 1.70	± 2.08	± 3.75	± 1.53	± 1.76	± 1.35
Range	26–64	23–65	16–73	21–56	38–82	52–77
Sex (male : female)	29 : 7	18 : 13	15 : 11	17 : 12	19 : 10	15 : 14
Mean NART IQ	97.16	101.27	97.26	98.39	100.47	100.81
± SEM	± 1.51	± 1.36	± 2.50	± 1.83	± 1.84	± 1.23
Range	83–114	79–117	77–116	79–113	79–115	91–115

SEM = standard error of the mean; NART = estimated premorbid NART IQ; Comparison 1 = schizophrenia patients and their matched control subjects versus patients with frontal and temporal lobe lesions; Comparison 2 = schizophrenia and their matched control subjects versus Parkinson's disease patients and their (older) matched control subjects. *$P < 0.0001$.

communicating aneurysm clipped, four had a right-sided meningioma removed, two were cases of arteriovenous malformation removal, two had astrocytoma removed, one case had craniopharyngioma removed). Eight patients had left frontal lobe excisions (four cases of unilateral lobectomy, one case of arteriovenous malformation removed, two had astrocytoma removed, one case had intra-cerebral haematoma evacuated). Three patients had bifrontal meningioma removal. The patients with frontal lobe lesions were tested, on average, 38 months postoperatively (median = 24 months, range = 1–240 months). Fifteen were on anticonvulsant medication at the time of testing.

Patients with temporal lobectomy/amygdalo-hippocampectomy. Data for patients with temporal lobe lesions who had undergone unilateral surgery for intractable epilepsy were derived from the sample described by Owen *et al*. (1991, 1995). Three patients were excluded because of histories of affective disorder (two patients) and substance abuse (one patient). Eighteen patients had undergone a standard 'en bloc' unilateral temporal lobe resection and 11 patients had had unilateral resection of medial temporal structures (amygdalo-hippocampectomy). Those temporal lobe patients who had had surgery to the dominant hemisphere had typically received smaller resections (1–2 cm) of the superior temporal gyrus, in order to reduce any effects on speech. In this standard operation usually up to one half of the amygdala was also removed as well as a small amount of hippocampus. Nine cases in the group with temporal lobe lesions had had left-sided surgery, with a mean resection (± SD) of 6.1 ± 0.63 cm (range, 4.5–7.0 cm), including resection of a portion of hippocampus (mean = 17.4 mm, range = 5–28 mm). Nine temporal lobe patients had a right temporal lobectomy with a mean resection (± SD) of 5.94 ± 0.391 cm (range = 5.0–6.5 cm) excised, including removal of hippocampus in four patients (mean = 20.75 mm, range = 20–23 mm). These patients were tested, on average, 35 months after surgery (range = 8–121 months). Patients in the amygdalo-hippocampectomy group (eight left-sided, three right-sided) received a variant of the 'en bloc' temporal resection, the selective amygdalo-hippocampectomy. This operation was performed in patients with a known structural lesion in or near the medial temporal structures or when other investigations have suggested a medial temporal focus for seizures. Amygdala and hippocampus were removed entirely on one side without any permanent damage to the overlying cortical structures. These patients were assessed, on average, 11.6 months after surgery (range = 5–24 months). All patients were on anticonvulsant medication. For the analyses below, the temporal and amygdalo-hippocampectomized patients were grouped together (temporal group).

All of the control subjects and neurological patients, as well as 33 of the schizophrenia patients in Comparison 1, completed the 'Tower of London' task to all levels of difficulty. Three patients with schizophrenia did not complete the five-move problems.

Comparison 2: schizophrenia versus Parkinson's disease

In the second comparison, the patients with schizophrenia were compared with a group of patients with Parkinson's disease. The same patients with schizophrenia and their control subjects (as described in Comparison 1) were compared with a group of 29 patients with Parkinson's disease. Because the latter were older than the schizophrenia group, a second control group of 29 subjects, matched to the Parkinson's disease patients, was also used. The characteristics of these patients and control subjects are shown in Table 1. The four groups were well-matched for NART IQ [$F(3,120) = 1.68$] and were not significantly different with regard to sex ($\chi^2 = 6.71$, $P < 0.1$). The

Parkinson's disease group and their older control subjects were significantly older than the schizophrenia group and their controls [$F(3,121) = 29.78$, $P < 0.0001$]. However, each patient group and their respective control group were well-matched for age.

Data for the Parkinson's disease patients were derived from the sample already described by Owen *et al*. (1992). The patients were diagnosed with idiopathic Parkinson's disease by a consultant neurologist, who also assessed the severity of the illness using the rating scale of Hoehn and Yahr (Hoehn and Yahr, 1967). The Parkinson's disease patients in the present study had mild or severe symptoms of the illness. The average duration of illness was 8.64 years and the mean Hoehn and Yahr score (± SEM) was 2.62 ± 0.17. They were all receiving L-dopa preparations (mean dose of L-dopa = 677 mg), while seven patients were also receiving anti-cholinergic medication (orphenadrine or benzhexol) at the time of testing. All the Parkinson's disease patients had Mini-Mental State Scores (Folstein *et al*., 1975) of >23, to exclude the possibility of clinical dementia. Six of the Parkinson's disease patients did not complete all problems from the 'Tower of London' task.

Neuropsychological assessments

Patients and control subjects were assessed with the National Adult Reading Test (NART; Nelson 1982), which provides an accurate estimate of premorbid intelligence level. This was converted to the Wechsler Adult Intelligence Scale—Revised intelligence quotient (WAIS-R IQ) (Wechsler, 1981) using standard tables or the formula available in the manual. For those patients with schizophrenia who scored <10 correct words on the NART, further testing was carried out using the Schonell Graded Word Reading Test (Schonell, 1942) which provided more accurate assessment of premorbid IQ at the lower levels.

Computerized neuropsychological assessment procedures

Patients and control subjects were assessed using tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Owen *et al*., 1990; Sahakian and Owen, 1992; Robbins *et al*., 1994*b*), a series of computerized tasks which were run on an Acorn BBC Master microcomputer with a high resolution Microvitec colour monitor and a Microvitec (Touchtec 501) touch sensitive screen. Subjects were seated ~0.5 m from the monitor and were required to respond by simply touching the screen with a finger. They first completed a 'motor screening task' (placing a finger on the centre of a flashing cross) which familiarized them with the testing procedure. After satisfactory completion of this task, subjects were given the tasks that are briefly described below. Detailed descriptions of these tests are provided elsewhere (Owen *et al*., 1990; Robbins *et al*., 1992).

Spatial short-term memory task (visuo-spatial span)

This computerized version of Corsi's block tapping test (Milner, 1971) assessed the subject's ability to remember a sequence of squares presented on the screen. For each trial, subjects observed a series of white squares that changed colour and were required to remember the location and sequential order of the squares that changed. The test commenced at a 'two-square' span level and, for each successful trial, the number of squares changing colour in the proceeding sequence was increased by one, to a maximum of nine squares. The visuo-spatial span was defined as the highest level at which the subject successfully remembered at least one sequence of squares. This measure was used to assess the ability of subjects to hold information 'on-line' in order to plan a series of moves in tasks such as the spatial working memory task and the Tower of London, described below.

Spatial working memory task

This task required subjects to 'search through' a number of boxes on the screen in order to locate blue tokens which were hidden inside the boxes. The key instruction was that once a token had been located behind a particular box, that box would not be used again to hide another token in the sequence. Since each box was only used once, on every trial the maximum number of tokens corresponded to the number of boxes on the screen. Subjects received four test trials with each of two, three, four, six and eight boxes. A 'within-search error' occurred when a subject searched any box more than once during the sequence, while a 'between-search error' was committed when a subject returned to search a box in which a token had already been found during a previous searching sequence. A 'strategy' score was calculated for subject performance for the more difficult six- and eight-box levels (Owen *et al*., 1990). This score reflected how often the subject initiated a searching sequence from the same box during the trial, indicating the ability to adopt a systematic searching approach. The measure was scored on a scale of 1 to 37, with lower scores indicating extensive use of the approach, and higher scores reflecting inefficient use of the strategy.

Planning task (computerized 'Tower of London')

This task was derived from the 'Tower of London' task developed by Shallice and McCarthy (Shallice, 1982). Subjects were presented with a problem where they were required to rearrange a set of balls in the bottom half of the computer screen, so that their positions matched the goal arrangement presented in the top half of the screen. The starting position of the balls was varied so that the minimum number of moves to solution was two, three, four or five moves. Subjects were instructed to examine the position of

the balls at the commencement of each problem and attempt to solve it in a specified minimum number of moves. Twelve copying trials were presented: two trials for each of the two- and three-move solutions, and four trials for each of the four- and five-move solutions. The accuracy measures during the copying trials consisted of the number of test trials completed within the minimum number of moves and the total number of moves in excess of the minimum. The program also recorded the planning ('initial thinking') and execution ('subsequent thinking') latencies during the copying trials to provide estimates of cognitive speed.

For each copying trial, a control condition was employed to provide a measure of motor initiation and execution times that were independent of thinking times. During these 'following' trials, subjects were instructed to follow a sequence of single moves executed in the top half of the screen, by moving the corresponding ball on the display presented on the lower half of the screen. Once the subject had made the appropriate move, the top arrangement would change again and the subject was required to make another single move. Subjects were prompted to make these single moves as quickly as possible. These 'following' trials acted as a control condition for the copying trials, as they were exact replications of the subject's earlier planning moves. The measurement of selection ('initial movement') and execution ('subsequent movement') latencies in the 'following' conditions provided the estimates of motor speed.

Data processing and analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS/PC) (Nie *et al.*, 1970). Latencies for the 'Tower of London' task were measured to the nearest 10 ms, and transformed into logarithms (base 10) to reduce skewness in the distribution and thereby meet the assumptions of the analysis method. Repeated measures analysis of variance was conducted using a two-factor design which included a between-subjects factor (group) and a within-subject factor (e.g. difficulty level). For Comparison 1, age was included as covariate in these analyses, as the group with temporal lobe lesions was significantly younger than the other groups. Within-group effects and interaction effects were examined using repeated measures analysis of variance within a MANOVA design (Wilk's Multivariate test of significance). *Post hoc* analyses were conducted using one-way analysis of variance and the Studentized Newman–Keuls procedure. Correlations were calculated using Pearson's product moment coefficient (r) or Spearman's rank correlation (r_s), as appropriate.

Results

Spatial short-term memory task (Table 2)

In Comparison 1, there was a significant difference in visuo-spatial span scores, with the schizophrenia group scoring significantly below all other groups [$F(3,114) = 11.70$, $P < 0.001$, with age as covariate]. In Comparison 2, the patients with schizophrenia scored significantly below the Parkinson's disease group and both control groups, while the Parkinson's disease group was impaired in comparison with the younger control subjects [$F(3,119) = 11.27$, $P < 0.0001$].

Spatial working memory task

Figure 1A and B show the mean number of 'between-search errors' for each group at various stages of the task for the two comparisons. For both Comparison 1 and Comparison 2, there was a highly significant difference between the four groups in their performance of the task in terms of the number of 'between-search errors' [for Comparison 1, $F(3,112) = 12.95$, $P < 0.001$, with age as covariate; for Comparison 2, $F(3,118) = 10.68$, $P < 0.001$]. There was also a significant main effect of task difficulty [for Comparison 1, Wilk's $\lambda = 0.161$, $F(4,110) = 143.42$, $P < 0.001$, with age as covariate; for Comparison 2, Wilk's $\lambda = 0.125$, $F(4,115) = 201.34$, $P < 0.001$] and significant group×difficulty interactions [Comparison 1: Wilk's $\lambda = 0.626$, $F(12,291.32) = 4.70$, $P < 0.001$, with age as covariate; Comparison 2: Wilk's $\lambda = 0.697$, $F(12,304.55) = 3.71$, $P < 0.001$] indicating that the magnitude of the difference between the groups increased as the task demands became progressively greater. For each study, the difference between the groups was investigated further using the Studentized Newman–Keuls test at each level of difficulty as well as comparing the total 'between-search errors' summed over all stages of the task.

In Comparison 1, there was no difference between the control group and that with temporal lobe lesions in the number of 'between-search errors' at each level of difficulty or in the total 'between-search errors' (*see* Table 2). For total 'between-search errors', the schizophrenic patients made significantly more errors than all other groups, including the group with frontal lobe lesions who, in turn, were significantly impaired in comparison with the control subjects and the group with temporal lobe lesions [$F(3,112) = 12.92$, $P < 0.001$, with age as covariate]. The schizophrenia group was impaired at all stages of the task in comparison with control subjects. Also, they differed from the group with temporal lobe lesions at all stages except 3, and differed from the patients with frontal lobe lesions at stages 4 and 8. The group with frontal lobe lesions differed from the control subjects and the group with temporal lobe lesions at stage 6.

In Comparison 2, the schizophrenia group was significantly impaired compared with the group of matched control subjects at all levels of difficulty [$F(3,118) = 10.67$, $P < 0.001$], and performed worse than the Parkinson's disease group and the elderly control subjects at stage 2 and 3. The Parkinson's disease group was impaired in comparison with the younger control subjects, but was not significantly different from their matched older control subjects. The latter were also impaired on this task in comparison with the younger control group.

Table 2 *Scores for the six groups of subjects (unadjusted means ± SEM) in the various tasks*

	Schizophrenia patients	Matched control subjects	Frontal lobe lesions	Temporal lobe/ amygdalo-hippo-campal lesions	Parkinson's disease (medicated)	Older control subjects
Visuo-spatial span	3.79 ± 0.16	5.10 ± 0.18	4.96 ± 0.23	5.46 ± 0.21	4.38 ± 0.17	4.72 ± 0.18
Spatial working memory (between- and within-search errors)						
Between	69.15 ± 4.30	36.87 ± 4.53	51.08 ± 4.37	33.81 ± 3.42	58.31 ± 4.17	53.10 ± 3.61
Within	10.45 ± 2.00	7.16 ± 2.61	12.04 ± 2.53	3.22 ± 0.58	6.86 ± 1.15	6.72 ± 1.66
Strategy	21.1 ± 0.59	16.2 ± 0.74	17.2 ± 0.88	15.5 ± 0.95	17.0 ± 0.87	17.5 ± 0.76
Tower of London: perfect solutions						
2 moves	1.9 ± 0.07	1.97 ± 0.03	2.0 ± 0.0	2.0 ± 0.0	1.82 ± 0.09	2.0 ± 0.0
3 moves	1.25 ± 0.12	1.68 ± 0.10	1.58 ± 0.11	1.83 ± 0.07	1.43 ± 0.15	1.41 ± 0.12
4 moves	2.0 ± 0.17	2.32 ± 0.20	2.15 ± 0.18	2.62 ± 0.18	1.85 ± 0.21	2.14 ± 0.17
5 moves	1.53 ± 0.17	2.06 ± 0.24	1.65 ± 0.21	2.41 ± 0.20	1.67 ± 0.23	1.55 ± 0.20
Tower of London: excess moves above minimum						
2 moves	0.22 ± 0.15	0.03 ± 0.03	0.0	0.0	0.46 ± 0.25	0.0
3 moves	1.33 ± 0.27	0.45 ± 0.16	0.62 ± 0.18	0.17 ± 0.07	1.46 ± 0.53	0.83 ± 0.22
4 moves	6.45 ± 0.79	6.42 ± 0.81	6.96 ± 0.87	5.0 ± 0.62	7.67 ± 1.17	7.03 ± 0.79
5 moves	10.75 ± 0.96	8.19 ± 1.24	10.35 ± 1.56	6.10 ± 1.0	10.11 ± 1.70	10.83 ± 1.23
Tower of London: number completed within maximum						
2 moves	1.97 ± 0.03	2.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0	1.89 ± 0.08	2.0 ± 0.0
3 moves	1.94 ± 0.04	1.97 ± 0.03	2.0 ± 0.0	2.0 ± 0.0	1.71 ± 0.13	1.97 ± 0.03
4 moves	3.03 ± 0.15	3.03 ± 0.16	2.92 ± 0.18	3.28 ± 0.10	2.81 ± 0.26	2.86 ± 0.17
5 moves	3.03 ± 0.15	3.39 ± 0.18	2.92 ± 0.24	3.59 ± 0.14	2.96 ± 0.26	3.10 ± 0.19
Tower of London: initial movement time (s)						
2 moves	8.54 ± 1.21	2.63 ± 0.21	3.38 ± 0.43	2.32 ± 0.18	4.03 ± 0.51	4.14 ± 0.48
3 moves	7.71 ± 1.89	2.32 ± 0.22	2.62 ± 0.26	2.31 ± 0.23	3.72 ± 0.39	3.42 ± 0.36
4 moves	6.23 ± 1.05	2.25 ± 0.25	2.53 ± 0.23	1.85 ± 0.09	3.65 ± 0.37	3.45 ± 0.37
5 moves	6.18 ± 0.84	2.10 ± 0.19	2.41 ± 0.24	1.81 ± 0.08	3.13 ± 0.35	2.82 ± 0.29
Tower of London: subsequent movement time (s)						
2 moves	7.06 ± 0.69	2.07 ± 0.12	4.53 ± 0.34	4.35 ± 0.29	3.21 ± 0.26	2.96 ± 0.29
3 moves	5.88 ± 0.65	2.23 ± 0.13	4.06 ± 0.36	3.18 ± 0.14	3.59 ± 0.35	2.95 ± 0.22
4 moves	5.88 ± 0.46	2.42 ± 0.13	3.54 ± 0.26	0.31 ± 0.12	3.86 ± 0.40	3.10 ± 0.22
5 moves	4.46 ± 0.29	2.38 ± 0.11	3.34 ± 0.33	2.76 ± 0.11	2.23 ± 0.20	3.36 ± 0.56
Tower of London: initial thinking time (s)						
2 moves	8.95 ± 3.13	2.09 ± 0.30	2.62 ± 0.45	2.92 ± 1.23	3.66 ± 0.66	3.07 ± 1.01
3 moves	13.01 ± 2.21	8.57 ± 1.23	14.48 ± 2.58	8.10 ± 1.22	15.40 ± 2.50	10.88 ± 1.21
4 moves	12.22 ± 1.89	8.10 ± 0.63	12.51 ± 2.27	11.53 ± 1.78	14.95 ± 2.09	8.60 ± 0.78
5 moves	9.20 ± 1.56	10.74 ± 1.41	14.11 ± 3.18	12.98 ± 1.24	16.12 ± 2.73	9.28 ± 1.09
Tower of London: subsequent thinking time (s)						
2 moves	4.33 ± 1.50	0.53 ± 0.22	1.66 ± 0.49	0.77 ± 0.33	2.35 ± 0.75	0.45 ± 0.18
3 moves	4.29 ± 1.15	0.80 ± 0.25	3.86 ± 1.59	1.24 ± 0.37	2.45 ± 0.94	1.68 ± 0.45
4 moves	5.01 ± 0.78	2.70 ± 0.49	6.82 ± 1.95	2.53 ± 0.37	3.22 ± 0.49	4.01 ± 0.57
5 moves	3.83 ± 0.64	1.90 ± 0.37	4.79 ± 1.24	2.04 ± 0.37	2.70 ± 0.48	2.81 ± 0.37

'Within-search errors' were variable and at a low level, hence analysis was performed by summing over the levels of difficulty to determine the total number of 'within-search errors' for each group (Table 2). The difference between the groups for the number of 'within-search errors' did not reach significance in Comparison 1 [$F(3,112) = 2.67$, $P = 0.051$, with age as covariate]. There was no significant difference between the groups in the number of 'within-search errors' on this task in Comparison 2 [$F(3,118) = 0.86$].

The measure of strategy in this task was scored on a scale of 1 to 37, with lower scores representing more efficient use of strategy. A score of one is achieved when, within each of the more difficult six- and eight-move problems, the same box is used to initiate each search sequence (Table 2). There was a significant difference in strategy scores between the groups in Comparison 1 [$F(3,111) = 8.69$, $P < 0.001$, with age as covariate]. *Post hoc* analysis revealed that this was due to the significantly reduced use of strategy in the schizophrenia group in comparison with the other groups. Strategy scores were also found to be significantly different between the groups in Comparison 2 [$F(3,116) = 9.20$, $P < 0.001$]. This was also due to the significant impairment in the use of strategy by the patients with schizophrenia.

The results from the 'spatial working memory' task indicate that patients with schizophrenia are impaired in their ability to complete the task, as evidenced by the greater number of

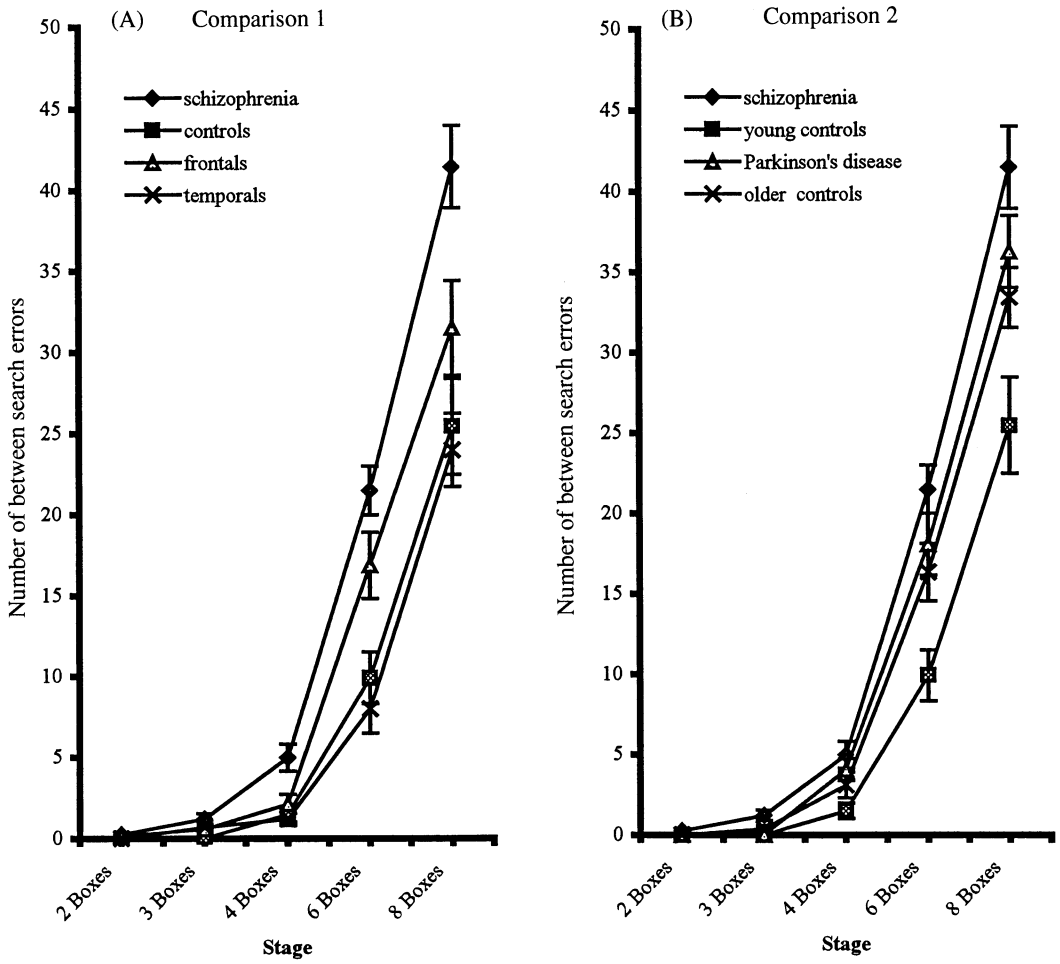

Fig. 1 The 'spatial working memory' task. The number of 'between-search errors' at each stage for (**A**) Comparison 1, (**B**) Comparison 2. Frontals = patients with frontal lobe lesions; temporals = patients with temporal lobe lesions.

'between-search errors', in comparison with control subjects and all the other neurological groups. The patients with frontal lobe lesions also made significantly more 'between-search errors'.

Planning task ('Tower of London')

For the computerized 'Tower of London' task the number of moves to solution was calculated for each group as well as the motor and thinking times.

Number of moves

The 'Tower of London' task consisted of a total of 12 problems. For each problem, three measures were determined relating to the number of moves to solution (Table 2), providing indices of efficiency or accuracy of performance on the task: (i) the proportion of problems solved within the minimum number of moves, (ii) the mean number of moves above the minimum possible, (iii) the number of problems solved within the maximum allowed.

(i) *Perfect solutions.* For Comparisons 1 and 2, the proportions of perfect solutions are shown in Table 2. In Comparison 1, there was a significant difference between the groups [$F(3,113) = 4.66$, $P < 0.01$, with age as covariate], a significant effect of increasing task difficulty [Wilk's $\lambda = 0.619$, $F(3,112) = 22.97$, $P < 0.001$], and an interaction effect between difficulty and group approached significance [Wilk's $\lambda = 0.862$, $F(9,272.73) = 1.91$, $P = 0.05$]. Analysis at each level of difficulty revealed that the schizophrenic patients completed significantly fewer perfect solutions at level 3 in comparison with all the other groups [$F(3,118) = 5.87$, $P < 0.001$], while the schizophrenia and frontal lobe lesion groups differed from the group with temporal lobe lesions at level 5 [$F(3,114) = 3.78$, $P = 0.01$]. This was confirmed when the total minimum move solutions across all tasks was examined, with the schizophrenia and frontal lobe lesion groups differing significantly from the group with temporal lobe lesions, while the schizophrenia group also solved fewer problems within the minimum moves than the control subjects [$F(3,113) = 4.66$, $P < 0.001$, with age as covariate]. In Comparison 2, the differences between the

groups in the number of perfect solutions were not significant [$F(3,115) = 2.05$].

(ii) *Excess moves.* The groups in Comparison 1 were significantly different in the number of moves above the minimum at each level of difficulty [$F(3,113) = 2.85$, $P < 0.05$, with age as covariate] (Table 2). The number of excess moves increased as the task became more difficult [Wilk's $\lambda = 0.248$, $F(3,112) = 113.45$, $P < 0.001$] and there was a significant group × difficulty interaction suggesting that the groups were differentially affected at the more difficult levels [Wilk's $\lambda = 0.835$, $F(9,272.73) = 2.34$, $P < 0.05$]. *Post hoc* analysis at each task level indicated that the schizophrenic patients differed from the other groups at level 3 [$F(3,118) = 6.81$, $P < 0.001$] and that the schizophrenia and frontal lobe lesion groups made significantly more moves above the minimum in comparison with the group with temporal lobe lesions at level 5 [$F(3,114) = 3.25$, $P < 0.05$]. When the total excess moves above the minimum were considered, the schizophrenia and frontal lobe lesion groups made significantly more excess moves than the group with temporal lobe lesions [$F(3,114) = 2.85$, $P < 0.05$, with age as covariate]. Thus, the schizophrenia and frontal lobe lesion groups required more moves above the minimum than other groups in attempting to solve the tasks and this discrepancy was more apparent as the task became more difficult.

There were no significant differences between the various groups in Comparison 2 [$F(3,115) = 0.87$], indicating that the number of excess moves was not different when schizophrenic patients were compared with Parkinson's disease patients (Table 2).

(iii) *Solutions within maximum moves allowed.* There were no significant differences between the groups in the total number of solutions completed within the maximum moves allowed at each level of difficulty for either Comparison 1 or Comparison 2 [for Comparison 1, $F(3,113) = 2.28$, $P < 0.10$, with age as covariate; for Comparison 2, $F(3,115) = 1.06$]. This suggests that the patients with schizophrenia as well as the other neurological patients were able to complete the problems successfully, though not necessarily efficiently.

In summary, the patients with chronic schizophrenia and the other neurological patients were able to complete as many problems as control subjects on the computerized 'Tower of London' task. However, the patients with schizophrenia and the patients with frontal lobe lesions solved significantly fewer problems within the minimum number of moves (i.e. fewer perfect solutions) and required significantly more moves above the minimum to achieve a solution, indicating that the efficiency or accuracy of their performance was inferior to those of other groups.

Latency measures

(i) *Movement times (Table 2).* The movement times for problem initiation (motor initiation time) and subsequent execution (motor execution time) were determined from the 12 'yoked control' trials of the 'Tower of London' task, as described earlier. In Comparison 1, there was a highly significant main group effect [$F(3,114) = 19.09$, $P < 0.001$, with age as covariate] indicating that there was a significant difference between the groups for initial movement time. There was a significant main effect of task difficulty on motor initiation time [Wilk's $\lambda = 0.761$, $F(3,113) = 11.83$, $P < 0.001$], but no significant group × difficulty interaction [Wilk's $\lambda = 0.963$, $F(9,275.16) = 0.48$]. As the task became more difficult the initial movement times tended to decrease in value for all groups, except for the group with temporal lobe lesions at level 4. Separate *post hoc* Studentized Newman–Keuls tests at each level of difficulty revealed that the schizophrenic patients differed from all other groups at each level of difficulty, while no difference was found between the other groups.

In Comparison 2, examination of the schizophrenia group compared with the Parkinson's disease patients together with their respective control groups revealed a significant main effect for motor initiation time [$F(3,111) = 14.20$, $P < 0.001$], a significant effect of task difficulty [Wilk's $\lambda = 0.827$, $F(3,109) = 7.59$, $P < 0.001$], but no significant interaction effect [Wilk's $\lambda = 0.938$, $F(9,265.43) = 0.79$]. Examination of each level of difficulty revealed that the schizophrenic patients were significantly slower than the other groups at all difficulty levels, while the Parkinson's disease group differed from the younger control group at all levels except 2. There was no significant difference between the Parkinson's disease patients and their matched older control group. The older control group differed from the younger control group at all levels except 5.

There was a significant main group effect for motor execution time in both Comparison 1 [$F(3,114) = 38.48$, $P < 0.001$, with age as covariate] and Comparison 2 [$F(3,111) = 28.89$, $P < 0.001$], also significant effects of difficulty [for Comparison 1, Wilk's $\lambda = 0.673$, $F(3,113) = 18.31$, $P < 0.001$; for Comparison 2, Wilk's $\lambda = 0.834$, $F(3,109) = 7.21$, $P < 0.001$] and significant group × difficulty interactions [for Comparison 1, Wilk's $\lambda = 0.628$, $F(9,275.16) = 6.45$, $P < 0.001$; for Comparison 2, Wilk's $\lambda = 0.740$, $F(9,265.43) = 3.89$, $P < 0.001$]. For each level of difficulty in Comparison 1, the schizophrenia group had significantly longer motor execution times compared with all other groups. The patients with frontal lesions were significantly different from control subjects at all difficulty levels, while the group with temporal lobe lesions differed at all stages except level 5. In Comparison 2, the schizophrenia group were again significantly slower in their subsequent movement times across all difficulty levels, while the Parkinson's disease patients and older control subjects differed from the younger control subjects but not from each other.

These data demonstrate that, in comparison with normal subjects and the other neurological groups, the patients with chronic schizophrenia were impaired in the sensorimotor

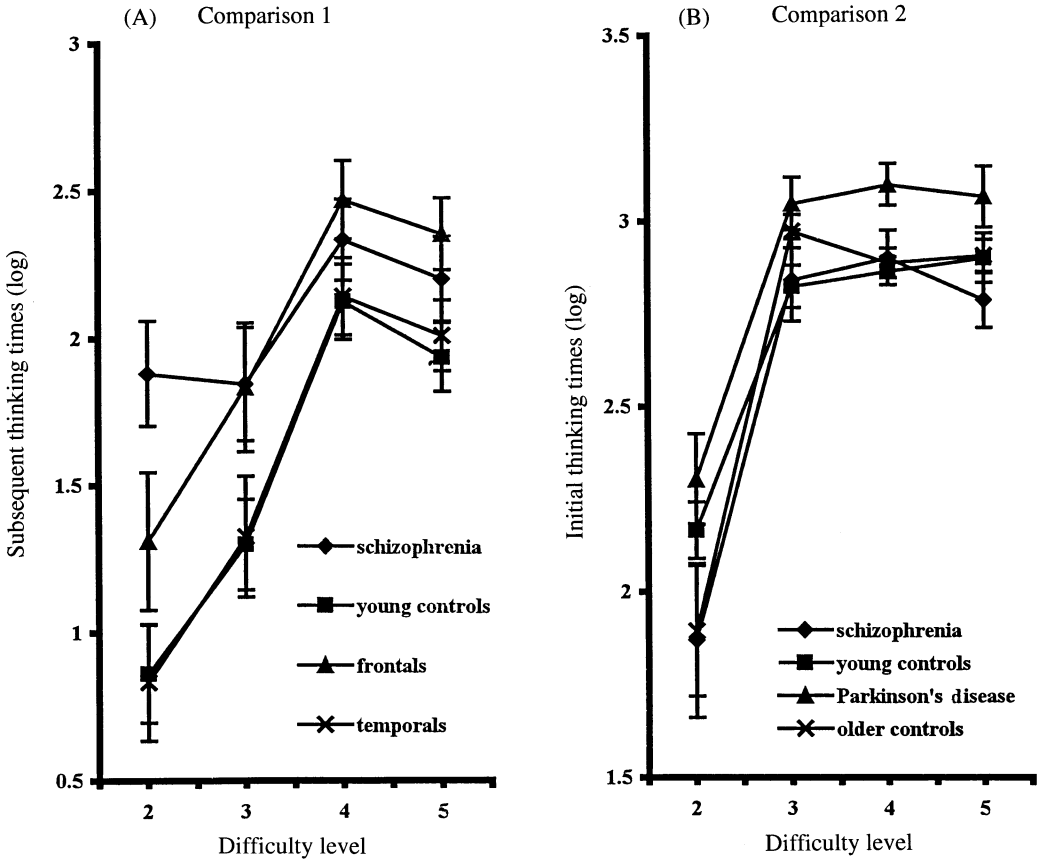

Fig. 2 The 'Tower of London' test: (**A**) 'subsequent thinking' times for patients and control subjects in Comparison 1, (**B**) 'initial thinking' (planning) times for patients and control subjects in Comparison 2. Latencies presented as logarithmic transformations (untransformed values appear in Table 2). Frontals = patients with frontal lobe lesions; temporals = patients with temporal lobe lesions.

requirements of the task involved in producing a sequence of single moves.

(ii) *Thinking times.* To assess the speed of cognitive processing, initial and subsequent thinking times were examined across each difficulty level of the computerized 'Tower of London' task (*see* Table 2 and Fig. 2A and B). In Comparison 1, we were particularly interested in subsequent thinking times in the schizophrenia group in comparison with the group with frontal lobe lesions, as such lesions have been shown to prolong subsequent, rather than initial, thinking time (Owen *et al*., 1990). This was confirmed in the present study, in which the group with frontal lesions had significantly longer subsequent thinking time in comparison with matched control subjects [$F(1,55) = 8.00$, $P < 0.01$], while initial thinking time was not significantly different [$F(1,55) = 0.06$]. In Comparison 2, we were comparing patients with schizophrenia and Parkinson's disease, as the latter have been demonstrated to have a specific impairment of initial rather than subsequent thinking time (Owen *et al*., 1992), in direct contrast to the pattern observed in the group with frontal lesions. This finding was also confirmed in the present study when Parkinson's disease patients were compared with their matched control subjects [significant difference in initial thinking time: $F(1,50) = 6.07$, $P < 0.05$; no significant difference in subsequent thinking time: $F(1,49) = 0.14$].

In Comparison 1, there was no significant difference between the groups for initial thinking time [$F(3,114) = 1.66$, with age as covariate]. However, the groups differed significantly in their subsequent thinking times (*see* Fig. 2A) [$F(3,113) = 5.28$, $P < 0.01$, with age as covariate], for which there was also a significant effect of task difficulty [Wilk's $\lambda = 0.487$, $F(3,112) = 39.32$, $P < 0.001$] but no significant group×difficulty interaction [Wilk's $\lambda = 0.923$, $F(9,272.73) = 1.01$]. Separate *post hoc* analyses were carried out at each difficulty level and for a composite measure of the mean subsequent thinking time across all levels. The schizophrenia and frontal lobe lesion groups differed significantly from the control and temporal lobe lesion groups, with the schizophrenic patients also being significantly slower than the frontal lobe lesion group [for composite mean subsequent thinking time: $F(3,116) = 6.04$, $P < 0.001$, with age as covariate]. Also, the schizophrenia group had slower subsequent thinking times than the frontal lobe lesion group at the simplest level of the task [level 2: $F(3,118) = 7.16$, $P < 0.001$] while the frontal lobe lesion group showed a trend

for a prolonged subsequent thinking time at the more difficult levels. Thus, the patients with schizophrenia and those with frontal lobe lesions were similar, in that both groups demonstrated a significantly prolonged subsequent thinking time, while the initial thinking time for both groups was not prolonged in comparison with that in control or temporal lobe lesion groups. However, the schizophrenia and frontal lobe lesion groups also differed, in that the schizophrenia group showed a prolonged subsequent thinking time at the earlier stages of the task.

In Comparison 2, there was a significant difference between the groups for initial thinking time (Fig. 2B) [$F(3,112) = 4.84$, $P < 0.01$] with a significant effect of difficulty [Wilk's $\lambda = 0.525$, $F(3,110) = 33.20$, $P < 0.001$], but no significant group × difficulty interaction [Wilk's $\lambda = 0.956$, $F(9,267.86) = 0.56$]. There was also a significant difference between the groups for subsequent thinking time [$F(3,111) = 4.56$, $P < 0.01$], with a significant effect of difficulty [Wilk's $\lambda = 0.439$, $F(3,109) = 46.50$, $P < 0.001$] and a non-significant trend for a group × difficulty interaction effect [Wilk's $\lambda = 0.872$, $F(9,265.43) = 1.70$, $P < 0.10$]. The summary scores for subsequent thinking time across tasks suggested that the differences were between the schizophrenia group and the other groups, although older control subjects were also slower than the younger control group [$F(3,114) = 8.42$, $P < 0.0001$]. As anticipated by the findings of Comparison 1, the schizophrenia group had a prolonged subsequent thinking time in comparison with the Parkinson's disease group, while the latter had a prolonged initial thinking time in comparison with both control subjects and patients with schizophrenia. However, separate analyses of subsequent thinking time at each level revealed that both the schizophrenia and Parkinson's disease groups had significantly longer subsequent thinking times at level 2 in comparison with both older and younger control subjects [$F(3,120) = 8.69$, $P < 0.0001$], while subsequent thinking time at the other levels were not significant.

In summary, while patients with chronic schizophrenia and patients with frontal lobe lesions had a tendency to spend less time planning a move to solution (i.e. initial thinking 'planning' time), they demonstrated significantly prolonged subsequent thinking times in comparison with other groups. This was in contrast to the Parkinson's disease patients who had significantly prolonged initial thinking or 'planning' times.

Correlational analyses

Inter-relationships among cognitive tests

Inter-relationships between measures of performance on each of the tasks were examined separately for each of the groups. As is seen in Table 3, in the normal subjects there were significant relationships between the various measures of executive function. The pattern of these relationships was significantly different in the frontal, Parkinson's disease and schizophrenia groups.

Inter-relationships between 'visuo-spatial span' and 'spatial working memory task' measures. In normal subjects, there were significant correlations between performance on the 'spatial working memory task', as measured by the number of 'between-search errors', and both spatial short-term memory span and strategy score, while short-term memory span and strategy were not significantly correlated. Thus, improved performance on this task was related both to greater short-term memory span and better strategy scores, with each contributing separately to performance. This relationship was also apparent in the group with temporal lobe lesions and the older control subjects. However, in the patients with frontal lobe lesions the relationship between strategy and performance on the 'spatial working memory task' was weakened, while the relationship with short-term memory span was greater, suggesting that patients with frontal lesions relied more heavily on short-term memory to perform the task. In contrast, patients with Parkinson's disease showed the opposite pattern; in this group 'spatial working memory task' performance was no longer significantly associated with short-term memory span, but was highly and significantly associated with strategy. Thus, patients with Parkinson's disease, who were impaired on the span task compared with younger control subjects, relied more heavily on strategy to perform this task. In patients with schizophrenia, who were the most severely impaired on strategy, performance on the 'spatial working memory task' was only found to be associated with spatial short-term memory span. Therefore, the relative contribution of either short-term memory span or strategy to the overall performance on the spatial working memory task differed across patient groups. While frontal lobe lesion and schizophrenia groups relied more heavily on short-term memory span rather than strategy, Parkinson's disease patients showed the opposite pattern.

When partial correlations were examined, using visuo-spatial span or strategy as covariates (as appropriate), the association between task performance on the 'spatial working memory task' and strategy remained non-significant in the schizophrenia group, became non-significant in the frontal lobe lesion group, but remained high in the other groups ($r > 0.46$, with visuo-spatial span as covariate). In contrast, the relationship between task performance and visuo-spatial span remained significant for the schizophrenia, temporal lobe lesion, Parkinson's disease and elderly control groups ($r \leqslant 0.45$, with strategy as covariate), while the association was no longer apparent in the young control and frontal lobe lesion groups. Thus, the markedly impaired use of strategy in the patients with schizophrenia was not associated with measures of impaired performance on the task, even after controlling for the effects of visuo-spatial span. Rather, visuo-spatial memory span was related to these measures, such that better scores for visuo-spatial span were associated with lower numbers of errors. In contrast, in the other groups, either strategy alone or both strategy and short-term spatial

Table 3 *Correlational analyses between measures on the CANTAB tasks, for each group*

Groups Tasks	Short-term memory span	Between search errors (SWMT)	Strategy score (SWMT)	Minimum move solutions (TOL)	Initial thinking time (TOL)
Young control subjects					
Between-search errors (SWMT)	–0.37*				
Strategy score (SWMT)	–0.29	0.64***			
Minimum move solutions (TOL)	0.35	–0.55**	–0.37*		
Initial thinking time (TOL)	0.24	–0.12	–0.14	0.25	
Subsequent thinking time (TOL)	0.20	0.49**	0.46**	–0.56***	0.35
Patients with schizophrenia					
Between-search errors (SWMT)	–0.47**				
Strategy score (SWMT)	–0.21	0.20			
Minimum move solutions (TOL)	0.06	–0.01	0.16		
Initial thinking time (TOL)	–0.08	0.39*	0.02	–0.26	
Subsequent thinking time (TOL)	–0.07	0.01	0.20	–0.46**	0.52***
Patients with frontal lobe lesions					
Between-search errors(SWMT)	–0.46*				
Strategy score (SWMT)	–0.41*	0.47*			
Minimum move solutions (TOL)	0.19	–0.42*	–0.45*		
Initial thinking time (TOL)	–0.34	0.13	0.03	0.25	
Subsequent thinking time (TOL)	–0.64***	0.61***	0.34	–0.36	0.45*
Patients with temporal lobe and amygdalo-hippocampal lesions					
Between-search errors(SWMT)	–0.59***				
Strategy score (SWMT)	–0.32	0.76***			
Minimum move solutions (TOL)	0.41*	–0.45*	–0.28		
Initial thinking time (TOL)	0.10	0.05	0.35	0.17	
Subsequent thinking time (TOL)	–0.38	0.50**	0.42*	–0.44*	0.48**
Medicated Parkinson's disease patients					
Between-search errors(SWMT)	–0.33				
Strategy score (SWMT)	–0.37	0.81***			
Minimum move solutions (TOL)	0.07	–0.34	–0.37		
Initial thinking time (TOL)	0.00	–0.18	–0.09	0.13	
Subsequent thinking time (TOL)	–0.26	–0.01	0.10	–0.47*	0.51*
Older control subjects					
Between-search errors(SWMT)	–0.40				
Strategy score (SWMT)	–0.39	0.49*			
Minimum move solutions (TOL)	–0.15	–0.24	–0.20		
Initial thinking time (TOL)	–0.03	0.16	0.24	–0.25	
Subsequent thinking time (TOL)	–0.34	0.51*	0.52*	–0.51*	0.41

Short-term memory span = visuospatial short-term memory span; SWMT = Spatial Working Memory Task; TOL = Tower of London Task. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

span were associated with performance on the 'spatial working memory' task.

These results suggest that the patients with schizophrenia could not rely on strategy, which was more severely impaired than in all other groups, to perform the 'spatial working memory' task, but relied on (an albeit impaired) spatial short-term memory.

Inter-relationships with 'Tower of London' task measures. With regard to the 'Tower of London' task, the main measures were intercorrelated with each other. Accuracy on the 'Tower of London' task was negatively and significantly associated with subsequent thinking time in all groups except the frontal lobe lesion group (Table 3). This suggested that the relationship between faster subsequent thinking time and greater accuracy was diminished in patients with frontal lobe lesions in comparison with other groups. In contrast, no associations were found between initial thinking times and accuracy measures. Positive correlations were apparent between initial and subsequent thinking times, suggesting that increased time to plan was associated with increased execution time. These relationships were most significant in the patient groups, particularly in the schizophrenia and Parkinson's disease groups, suggesting an overall slowness to complete the task.

Inter-relationships between 'Tower of London' task and other measures. As seen in Table 3, the performance on the 'Tower of London' task was significantly associated with measures from the 'spatial working memory task'. There

was a significant association between performance on the two tasks in normal subjects, such that better performance on the 'spatial working memory task' and better use of strategy were associated with better and faster performance on the 'Tower of London' task. In the frontal group a different pattern emerged. Strategy score was still associated with better 'Tower of London' task performance; however, the relationship with speed was no longer significant but, instead, was highly and significantly associated with spatial span score. This suggested that, in this patient group, short-term memory span was important for efficient performance on the 'Tower of London' task. In the temporal lobe lesion group and older control group, as in the younger control subjects, strategy score and better performance on the 'spatial working memory task' predicted efficient 'Tower of London' task performance. However, span was associated with improved performance on the 'Tower of London' task in the temporal lobe lesion group. In contrast, for the schizophrenia and Parkinson's disease groups, there were no associations between short-term memory span, or strategy, and the 'Tower of London' task performance.

Subject characteristics and cognitive measures

In the patients with schizophrenia, higher premorbid NART-estimated IQs were associated with higher scores for visuo-spatial span ($r = 0.38$, $P < 0.05$) but with no other task variable. Lower visuo-spatial span scores were also associated with increasing age ($r = –0.35$, $P < 0.05$), and with increased length of all hospital admissions ($r = –0.36$, $P < 0.05$, after controlling for age). Total length of all admissions was not associated with any other cognitive variables. Lengths of illness and lengths of current hospital admission were not associated with task performance on any of the cognitive measures after controlling for age. Increasing age was associated with lower levels of neuroleptic medication, expressed as milligram equivalents of chlorpromazine ($r_s = –0.51$, $P < 0.01$). The levels of medication were not associated with performance on any of the cognitive tasks. For the patients with Parkinson's disease there was a significant relationship between the severity of their illness and visuo-spatial span scores, indicating that patients with more severe illness had lower visuo-spatial span ($r = –0.37$, $P < 0.05$).

Discussion

In the present study, we directly compared cognitive performance of a large sample of patients with chronic schizophrenia with that of matched patients with neurosurgical lesions of the frontal and temporal neocortices and with a group of patients with Parkinson's disease, using tests of executive function which had previously been shown to be sensitive to the integrity of the frontostriatal circuitry. These tests included tasks which assessed different aspects of working memory (spatial span and spatial working memory tasks), including the ability to hold information on-line and the ability to manipulate such information; as well as tests which assessed planning ability and both motor and cognitive speed (computerized Tower of London task). This represents one of the few studies to date that have systematically compared schizophrenia with neurological disorders. The schizophrenia group was impaired on all three of these tasks in comparison with matched control subjects. While some of these deficits were apparently unique to schizophrenia, the pattern of results was qualitatively similar to the impairments found in the patients with focal frontal lobe lesions and, to a lesser extent, similar to those found in the patients with Parkinson's disease. In contrast, there were no similarities on these tests between the performance of the patients with schizophrenia and of patients with focal temporal lobe lesions, which included lesions of the hippocampus and amygdala. These findings thus provide support for the notion of schizophrenia as a disorder involving frontostriatal circuits. The deficits in executive functioning identified in this study could not be attributable to involvement of medial temporal lobe structures.

Spatial short-term memory and spatial working memory deficits in schizophrenia

The spatial span task involves the ability to hold information (a sequence of moves) 'on-line' and this task provides a measure of spatial short-term memory capacity (cf. Baddeley, 1986). In contrast, the spatial working memory test is a self-ordered task of increasing difficulty which involves at least two important components of 'working memory', namely the holding of information 'on-line' and the performance of other cognitive operations involving this information (*see* Robbins, 1996). In the present study, the patients with schizophrenia were impaired on both of these tasks. For the spatial span task, patients with schizophrenia had lower scores compared with all other neurological groups and with matched control subjects. Patients with Parkinson's disease were also impaired in their performance on this task in comparison with the younger control group, and increased severity of Parkinson's disease was associated with lower span scores. This is consistent with the previous findings of Owen *et al*. (1992) that identified impairments on this task in the more severely affected patients with Parkinson's disease. Thus, the patients with chronic schizophrenia were particularly impaired in their capacity to hold information 'on-line', in agreement with other results (Park and Holzman, 1992; Fleming *et al*., 1997). However, there was a preserved capacity to avoid 'within-search' errors in the self-ordered spatial working memory task, which indicates some residual ability to use on-line processing for performing self-generated response sequences.

The main results of the self-ordered 'spatial working memory' test identified significant differences between the groups in their performance on this task, as measured by the number of 'between-search errors', and the magnitude of the

difference between the groups was accentuated as the task demands progressively increased. The patients with schizophrenia showed the most severe deficit in performance on this task in comparison with all other groups (*see* Fig. 1). The older control subjects and Parkinson's disease patients were impaired in comparison with the younger control subjects, as expected from the results of Owen *et al*. (1992). The patients with frontal lobe lesions also showed significant deficits in their performance on the 'spatial working memory' task (cf. Owen *et al*., 1992, 1996*c*), while the temporal lesioned group were unimpaired on this task (cf. Owen *et al*., 1995). Previously, Owen *et al*. (1996*c*) identified distinct deficits in the patients with frontal and temporal lobe lesions; the former group demonstrated marked deficits on the same task of spatial working memory as that used in the present study, while the temporal lobe patients were most severely impaired on a similar task of visual working memory. While in the present study only spatial working memory was assessed, the results suggest that the patients with schizophrenia were more similar to patients with frontal lobe lesions and Parkinson's disease rather than to patients with temporal lobe/amygdalo-hippocampal lesions. Future studies will need to compare these groups on tasks of visual as well as spatial working memory.

Performance on the spatial self-ordered working memory task has previously been found to be related to either the ability to develop a systematic strategy during task performance or to holding information 'on-line' in a visuo-spatial scratch pad, as measured in the spatial span task (Owen *et al*., 1990; Robbins, 1996). Strategy was measured during the task by assessing the use of a systematic approach for solving the more difficult six- and eight-move problems. For the patients with schizophrenia, there was a marked and significant impairment in the ability to develop a systematic strategy to perform the task. The patients with Parkinson's disease did not show any deficit in strategic ability, confirming a previous study (Owen *et al*., 1992). While a deficit in strategy has been demonstrated in patients with frontal lobe lesions (Owen *et al*., 1990, 1996*c*), no such deficit was apparent in the present study which used a subset of these patients, but compared them with a different control group. The likely cause of this apparent discrepancy is that the control subjects used here had lower WAIS scores than the high functioning group with frontal lobe lesions (both NART IQ and WAIS scores are reported by Owen *et al*., 1992). The strategic deficit in planning in patients with frontal lobe lesions has recently been confirmed in an independent study which used a virtually identical task (Miotto *et al*., 1996). The latter study and our own unpublished observations (R. Rogers and T.W.R., unpublished results) have shown that right sided lesions produce significantly greater deficits of strategic ability. Thus, the heterogeneity within the group with frontal lobe lesions may also contribute to the present failure to repeat the original findings of impaired strategy. Notwithstanding, the deficits in strategic processing shown here by the schizophrenia group are highly robust and reliable, perhaps indicating the profound influence of the schizophrenic disorder on frontal lobe function, rather than temporal lobe or basal ganglia function. The results are unlikely to be a consequence of the NART estimated premorbid IQ representing an underestimate of the true potential of patients with schizophrenia (as suggested by some studies; e.g. Wolf and Cornblatt, 1996) as that would act to minimize group differences.

It is also evident that the frontal deficit on the spatial working memory task is not merely attributable to impaired strategy as pointed out by other authors (Miotto *et al*., 1996; Owen *et al*., 1996*c*; Robbins, 1996). The correlational analyses revealed that the relative contributions of spatial span and strategy to the performance on the 'spatial working memory' task differed for each of the neurological patient groups and normal control subjects. In normal subjects, both span and strategy contributed independently to performance, as indicated by the lack of correlation between these measures. This pattern changed in the other groups, with span and strategy being more, or less, important to task performance, particularly where groups were differentially impaired on one or other of these measures. In the frontal lobe lesion and schizophrenia groups there was a significantly greater contribution of short-term memory span to performance of the task. This was particularly evident in schizophrenia, where there was no contribution from strategy to task performance, even after controlling for the effects of the diminished visuo-spatial span in these patients. In contrast, the performance of Parkinson's disease patients was related to strategic ability rather than visuo-spatial short-term memory. This group exhibited an impaired spatial span compared with young control subjects and poorer span performance was associated with greater severity of illness, while no deficit in strategy was apparent. Thus, while patients with schizophrenia and Parkinson's disease showed impaired visuo-spatial span, the schizophrenia group necessarily relied on their impaired visuo-spatial span ability to perform the task, as the strategic deficit was severe.

Therefore, both impaired strategy and reduced capacity of short-term spatial memory contributed to performance of the self-ordered task in the different patient groups, with deficits in these being most marked in the patients with schizophrenia. This form of self-ordered 'spatial working memory' test has not been used previously in the assessment of cognitive function in patients with schizophrenia. Working memory deficits have been reported in schizophrenia using ocular motor and tactile tasks to index spatial working memory (Park and Holzman, 1992, 1993). However, the tests used in those studies only required subjects to hold spatial information 'on-line' in short-term memory, not to manipulate the information via a central executive as in the present study.

Deficits of working memory have been implicated in disorders affecting prefrontal areas, including the dorsolateral prefrontal cortex (Goldman-Rakic, 1987; Petrides, 1995). The dorsolateral prefrontal cortex has been suggested to be dysfunctional in schizophrenia as shown by deficits during

cognitive activation under PET (Weinberger *et al*., 1986, 1988). However, more recent evidence suggests that there are two important executive processing systems within the lateral frontal cortex (Petrides, 1994), which are important components necessary for the working memory tasks used in the present study. Petrides (1994) suggests that the active comparison of stimuli held in short-term memory and the active sequential organization of responses is subserved by the middle portion of the ventrolateral frontal cortex (Brodmann areas 45 and 47). In contrast, the active manipulation and monitoring of information within working memory requires the integrity of the mid-dorsolateral frontal cortex (Brodmann areas 46 and 9).

In a recent PET study Owen *et al*. (1996*b*) investigated these components of working memory using tasks derived from the same spatial working memory and spatial span tasks used in the present study. The spatial span task was shown to activate the ventrolateral prefrontal cortex (area 47), while the spatial working memory task resulted in activation of the mid-dorsolateral prefrontal cortex (areas 46 and 9). This study suggested that the dorsolateral frontal cortex subserves the executive functions of monitoring, organizing and executing a sequence of selections. Our findings thus support the notion that, in schizophrenia, both ventrolateral and dorsolateral frontal circuits are compromised (as well as their interaction). These findings are consistent with previous PET findings of hypofunctioning of dorsolateral prefrontal cortex in patients with schizophrenia (Weinberger *et al*., 1986). However, our results also implicate ventrolateral prefrontal areas, suggesting that other prefrontal areas may also be important in this disorder.

Deficits in planning in schizophrenia

In the 'Tower of London' task, subjects were required to plan the moves from an initial position to a target position as quickly and efficiently as possible. The task was first developed to assess the ability to plan and execute the solution to a novel task, and was found to be sensitive to frontal cortical lesions (*see* Shallice, 1982, 1988). While the original version required subjects to complete each task within a specified time period, the computerized version used in the present study did not impose a time limit. Instead, using a 'yoked' control condition, both movement and thinking latencies were assessed. The latter have proved useful in evaluating differences between patients with frontal lobe lesions and those with basal ganglia disorders (Owen *et al*., 1992).

In the present study, the patients with chronic schizophrenia and the other neurological patients were able to solve as many 'Tower of London' problems as control subjects, indicating that there were no gross deficits. However, the patients with schizophrenia and the patients with frontal lobe lesions solved these problems inefficiently, using more moves to complete the problems and producing fewer perfect solutions. Thus, for these groups the efficiency or accuracy of their performance was inferior to other groups and these deficits were increasingly apparent as the task became more difficult.

The pattern of effects for thinking latency in the schizophrenia group was qualitatively similar to that of the group with frontal lobe lesions, with no impairments in the latency to initiate a planned sequence of moves, but a prolongation of the time taken to complete the problems (subsequent thinking time). Previously, this pattern has been interpreted as resulting from a tendency to produce solutions before they are fully planned with the result that the subjects have to pause during the task for further planning and greater 'monitoring' of the solutions (cf. Owen *et al*., 1990). One possibility for the patients with schizophrenia was that they were unable to hold information 'on-line' in order to plan a series of moves, a deficit also suggested by the impairments in spatial span and spatial working memory of this group. However, there was no correlation between measures of performance on this task and either visuo-spatial span or other aspects of working memory in the patients with schizophrenia, and other forms of cognitive deficit may have contributed.

Like the patients with frontal lobe lesions, the schizophrenia group was generally slower to make the movements required in the planning component of the task, as shown in the yoked motor control test (*see* Table 2), and this was taken into account in the estimates of thinking time described above. It is of interest that the schizophrenia group was slower on this task than the neurological patient groups, even including the Parkinson's disease group. This is probably not simply a product of greater motor deficit but greater impairment on the sensorimotor aspects of the yoked-control test, reminiscent of a simple 'continuous performance test' of attention, which is known to be sensitive to deficits in patients with schizophrenia (Cornblatt *et al*., 1989; Nuechterlein *et al*., 1994).

While the frontal lobe lesion and schizophrenia groups showed a pattern of prolonged subsequent thinking times, the Parkinson's disease group had prolonged initial thinking times (cf. Owen *et al*., 1990, 1992). This suggests that the frontal lobe lesion and schizophrenia groups tended to spend less time planning the solution to a problem. However, whereas patients with frontal lobe lesions had longer subsequent thinking latencies as the task became more difficult, the schizophrenia and Parkinson's disease groups had significantly prolonged subsequent thinking latencies even with the simplest two-move problems of the task which they were able to solve efficiently. Thus, though the findings suggest that patients with schizophrenia behave like patients with frontal lobe lesions with a specific impairment of subsequent rather than initial thinking time, the pattern observed for subsequent thinking time bears some limited similarity with Parkinson's disease patients. Further, initial and subsequent thinking times were highly correlated within the schizophrenia and Parkinson's disease groups, suggesting there was an overall cognitive slowness, or 'bradyphrenia',

for these patient groups. Bradyphrenia has been considered a characteristic feature of basal ganglia disorders (Cummings, 1986), and so this evidence for long thinking latencies in patients with schizophrenia provides support for the notion that subcortical structures or frontal–striatal–thalamic circuits are involved in this disorder (e.g. Early *et al*., 1987; Nelson *et al*., 1990; Robbins, 1990; Buchsbaum *et al*., 1992; Pantelis *et al*., 1992).

Previous studies of performance on the 'Tower of London' task in patients with schizophrenia have also reported impaired accuracy but few of these studies have obtained accurate estimates for thinking latency. One other recent study, using a non-computerized version of the 'Tower of London', confirmed that patients with schizophrenia did not differ from control subjects in their planning time, though in this study no assessment of subsequent thinking time was available (Hanes *et al*., 1996*a*). In the only other study to examine planning and execution times in patients with schizophrenia, Morris *et al*. (1995) also employed a computerized version of the 'Tower of London'. They examined a group of consecutive admissions to a psychiatric hospital, that constituted a less chronic population than those in the present study. Their results are consistent with the present findings of prolonged execution times, rather than initiation latencies, in comparison with control subjects. The authors suggested that these findings were similar to the deficits observed in patients with frontal lesions. However, in contrast to the present study, no direct comparison was made with other neurological groups with pathology affecting frontal regions or basal ganglia. Further, these studies did not examine the inter-relationships between performance measures on the 'Tower of London' nor did they assess the interrelationship with other tasks tapping executive function.

In the present study, the pattern of inter-relationships between measures of performance on the 'Tower of London' planning task and the other executive measures differed between the various patient and control groups. The changed pattern of relationships suggested that each group depended on a different balance of cognitive operations to assist in successful completion of the planning task (*see* Table 3). In the normal subjects, better spatial working memory performance and enhanced ability to generate an effective strategy were associated with more accurate and faster performances on the 'Tower of London' planning task. In the frontal and temporal lobe lesion groups, spatial working memory ability was also associated with better and faster ability on the planning task. In the frontal lobe lesion group, however, greater short-term memory capacity was associated with a faster speed on the planning task, while strategy remained important to more efficient performance. In contrast, for the temporal lobe lesion group, greater short-term memory capacity was related to more efficient performance while strategic ability was associated with faster speed. In the older control subjects, better spatial working memory performance and impaired strategy predicted slower performance on the planning task, but they were not related to measures of efficiency. The findings in these groups contrasted with the findings in patients with schizophrenia and Parkinson's disease for whom there were no significant associations between these measures of spatial working memory and spatial short-term memory and the measures of planning ability on the 'Tower of London task'. These findings in schizophrenia indicate a 'loosening' of relationships between task components which may represent a loss of supraordinate executive or supervisory operations, possibly corresponding to recent evidence of disordered functional connectivity in schizophrenia (McGuire and Frith, 1996).

Implications for neural substrates of functional deficits

The hypothesis of disordered functional connectivity can be pursued further with the aid of neuroimaging studies, particularly as all of the tests described in this study have been investigated in a functional activation context using PET or single photon emission computerized tomography (SPECT) (Morris *et al*., 1993; Rezai *et al*., 1993; Owen *et al*., 1996*a*, *b*). Some of these studies have identified neural systems activated by these tasks which overlap to a considerable extent (Owen *et al*., 1996*a*, *b*). These systems include discrete regions of the prefrontal cortex, as well as the striatum. Thus, a likely cause for the significant deficits in schizophrenia on these tests is the dysfunction of one or more elements in the neural systems, or because of a lack of 'functional connectivity' of the system as a whole (McGuire and Frith, 1996). While recent authors have proposed that corticocortical disconnections involving prefrontal cortex and medial temporal lobe structures (Goldman-Rakic, 1990; Weinberger, 1991; McGuire and Frith, 1996) or frontal–subcortical deafferentation (Pantelis *et al*., 1992) may explain the deficits in executive function in schizophrenia, our data would be consistent with a lack of the normal 'connectivity' between a number of prefrontal cortical areas (or their associated circuits). Further, the lack of deficits on the tasks of executive function, including working memory, in the patients with lesions in medial temporal lobe structures does not strongly support the suggestion of Weinberger (1991) and Goldman-Rakic (1990), that working memory deficits in schizophrenia involve dysfunctional interactions in connections between prefrontal cortex and the medial temporal lobe. Rather, our data suggest that, for some tasks involving working memory such as the self-ordered spatial working memory task and the 'Tower of London' task, the interactions may involve other structures such as fronto-parietal or frontostriatal circuitry. These results and conclusions are also consistent with the findings of Gold *et al*. (1994), who compared a group of patients with schizophrenia with patients with right- and left-sided temporal lobe epilepsy, on a comprehensive neuropsychological test battery.

The greater deficit in the schizophrenia group compared

with the frontal excision patients could derive from either of the above explanations, or stem from the fact that the excision patients had discrete, but also highly variable, lesions (Owen *et al*., 1990). Further studies to investigate the nature of the deficits in schizophrenia would thus benefit from comparisons with patients with frontal lobe lesions with more homogeneous lesion sites. By thus enabling a 'fractionation' of the prefrontal cortex into functionally separable areas (Shallice, 1988; Shallice and Burgess, 1991*a*, *b*) the underlying pathophysiological substrates of schizophrenia may be identified (Pantelis and Brewer, 1995, 1996; Brewer *et al*., 1996*a*).

Relationship between neuropsychological deficits and clinical measures in schizophrenia

Of the cognitive impairments of executive function identified in this study, only spatial short-term memory span was associated with any of the illness related variables. Lower scores for spatial short-term memory were associated with longer length of hospitalization rather than length of illness, suggesting that increased length of hospital stay was associated with the degree of deficit. While these findings could be interpreted to suggest that increased length of hospitalization contributed to cognitive impairment, a more likely explanation would be that impaired cognition is predictive of increased periods in hospital. This is consistent with the findings in first-episode patients, that executive deficits are apparent from the outset of illness (Hoff *et al*., 1992; Brewer *et al*., 1996*b*), and with the findings from longitudinal studies (for review, *see* Barber *et al*., 1996). Further, in our group of hospitalized patients, no relationship was found between any of the cognitive measures and current dosage of medication, suggesting that current antipsychotic dosage did not explain these deficits. This is also consistent with the findings of significant neurocognitive deficits in unmedicated first-episode patients (Bilder *et al*., 1992; Hoff *et al*., 1992; Saykin *et al*., 1994; Brewer *et al*., 1996*b*) and with the data from studies examining the effects of medication on cognition (for review, *see* King and Green, 1996). Thus, the present findings of impaired executive functioning using computerized laboratory tests have a considerable degree of clinical significance, suggesting that poor performance in some aspects of executive function is associated with poorer outcome, including longer periods of hospitalization.

Conclusion

In summary, we have found profiles of cognitive deficit in chronic schizophrenia which are similar to those associated with frontal lobe or basal ganglia dysfunction. By using a variety of measures and test components we have been able to provide a quite detailed characterization of the nature of the deficits on particular tests that enable definitive comparisons with other patient groups. We have demonstrated marked deficits in spatial short-term memory, spatial working memory, the ability to generate an effective strategy, and also marked deficits on a task of planning ability which included measures of both motor and cognitive speed. We have demonstrated, in patients with schizophrenia, that there is a 'loosening' of the association between different aspects of cognitive function, with evident similarities to patients with lesions of the prefrontal cortex or Parkinson's disease. These results implicate frontostriatal circuitry in the cognitive deficits observed in schizophrenia.

While few of the deficits observed during these tests were present in the patients with temporal lobe lesions, this does not necessarily imply, of course, that the patients with schizophrenia exhibit no temporal lobe-like cognitive features. In a parallel series of studies we have employed tests of visual memory and learning, sensitive to temporal lobe lesions, to investigate this same group of patients with schizophrenia. Further, the relationships of each of these sets of frontostriatal and 'temporal-like' cognitive deficits in schizophrenia have to be defined with respect to distinct clinical profiles, an issue to be explored in further analyses of these data.

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