Executive dysfunction in first-episode schizophrenia and relationship to duration of untreated psychosis: the West London Study*

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Background Many studies have demonstrated early generalised cognitive impairment in schizophrenia.

Aims To examine executive function in first-episode schizophrenia, characterise the nature of the impairment and specify any relationships with symptoms and duration of untreated psychosis (DUP).

Method Patients (n=136) and normal controls (n=81) were assessed with the Cambridge Automated Neuropsychological Test Battery, National Adult Reading Test IQ, and Scales for the Assessment of Positive and Negative Symptoms.

Results Memory and executive impairments in patients were independent of IQ level. Spatial working memory was impaired because of inadequate strategy use. On a planning task, patients showed reduced planning times and suboptimal problem-solving. On an attentional set-shifting task, 75% of patients were able to perform an extra-dimensional shift thought to be a core attribute of prefrontal cortex function. Those who failed had significantly longer DUP.

Conclusions Prefrontal cortex function deteriorates at the onset of psychosis and continues to worsen over time.

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The presence of cognitive dysfunction early in the course of schizophrenia is well documented (Bilder *et al*, 1992, 2000; Hoff *et al*, 1992; Saykin *et al*, 1994; Albus *et al*, 1996; Hutton *et al*, 1998; Mohamed *et al*, 1999). Most studies describe a general impairment which differs from that of chronic patients only in degree (Saykin *et al*, 1994). Many first-episode studies have used large batteries of neuropsychological tests and have derived global measures of function. Although this strategy produces robust measures, information concerning the specific nature of cognitive impairment is lost (Hutton *et al*, 1998). We therefore examined neuropsychological performance in detail using the Cambridge Automated Neuropsychological Test Battery (CANTAB), which allows decomposition of performance into more fundamental cognitive processes (Hutton *et al*, 1998). In a small group of first-episode patients we found a specific profile of executive impairment that differed from that of chronic patients (Elliott *et al*, 1995, 1998; Pantelis *et al*, 1997). We now report our findings in a larger group of patients. We also explored the effect of chronicity on cognitive function by examining the relationship between neuropsychological performance and duration of untreated psychosis.

METHOD

Subjects

Patients (n=136) were recruited as soon as possible after presentation to mental health services. The catchment population included deprived inner-city and relatively affluent suburban areas of west London, UK. The patients eligible for the study were aged between 16 and 50 years, were presenting to mental health services with a schizophreniform psychosis for the first time and had received no more than 12 weeks of antipsychotic medication. In each case the diagnosis was determined according to DSM–IV (American Psychiatric Association, 1994) criteria at regular review meetings held by two experienced clinicians (E.J., T.B.). A total of 95% of the subjects fulfilled the diagnostic criteria for schizophrenia and the remainder, for schizophreniform disorder. Normal volunteers (n=81) served as controls and were recruited from the same catchment area by advertising in local job centres and hospitals. Exclusion criteria were a history of mental illness themselves or in their first-degree relatives, the presence of a medical illness which might impair cognitive function and a history of alcohol or drug misuse. Permission to conduct the study was obtained from Riverside, Merton, Sutton and Wandsworth, Kingston and Richmond and Ealing, Hammersmith and Fulham Local Research Ethics Committees. Patients and controls gave written informed consent. Data from 30 patients and 30 controls have been presented previously (Hutton *et al*, 1998).

Clinical assessments

Patients were assessed on recruitment with the Scales for the Assessment of Positive Symptoms (SAPS; Andreasen, 1981) and Negative Symptoms (SANS; Andreasen, 1983). Scores for positive, disorganisation and negative syndromes of schizophrenia (Liddle & Barnes, 1990) were calculated for each patient by summing the SAPS and SANS global sub-scale scores pertaining to each factor. Duration of untreated psychosis (DUP) was established for each patient by reviewing relevant information in the case notes, and questioning the patient and relatives and/or carers. A modified questionnaire (Loebel *et al*, 1993) was used, relating to the onset of positive psychotic symptoms (Lieberman *et al*, 1993).

Cognitive function

In order to test as wide a range of patients as possible and to reduce state effects, neuropsychological assessments were undertaken when the patient was able to co-operate with the requirements of the testing procedure, usually once they had been medicated. To examine the specificity of frontal executive impairments, IQ and memory were also assessed. The National Adult Reading Test (NART) was used to estimate IQ (Nelson & Willison, 1991). Several subjects in both groups declined to take this test because of dyslexia or other reading problems. IQ was obtained for

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110 patients and 73 controls. CANTAB tests of memory and executive function were administered on an IBM-compatible PC with a touch-sensitive screen (Sahakian & Owen, 1992).

Spatial span (Owen et al, 1990)

This measured the ability to remember the order of sequences of squares presented on the screen in increasing number. This task was completed by 135 patients.

Pattern and spatial recognition memory (Sahakian et al, 1988)

In the pattern recognition test, 12 abstract visual stimuli were presented sequentially on the screen. Each stimulus was then presented along with a novel stimulus and the subjects were asked to touch the familiar stimulus. This was repeated with 12 different stimuli, giving a maximum possible score of 24. In the spatial task, five identical squares were presented in series, each in a different location. One square was then presented at each target location along with a square at a novel location. Subjects were asked to touch the square at the location they recognised from the learning phase. Four such trials using different locations were administered, giving a maximum possible score of 20. These tasks were completed by 132 patients.

Spatial working memory (Owen et al, 1990)

Subjects were required to 'open' sets of boxes, varying between three and eight in number, to find tokens. Errors were recorded when boxes in which tokens had been found were reopened. A common strategy employed in the performance of this task is to follow a predetermined sequence, beginning with one box and returning to start each new search with that box after a token has been found. A measure of this strategy was derived by counting the number of search sequences starting with the same box at the six- and eight-box stages. All patients completed this task.

Planning (Owen et al, 1990)

In this modification of the Tower of London task (Shallice, 1982), subjects moved coloured 'balls' in an arrangement displayed on the screen to match a goal arrangement. Subjects were asked to attempt the solution in the minimum number of moves, which could be 2, 3, 4 and 5. For each problem, a yoked control condition provided measures of motor initiation and execution times. As a stringent measure of accuracy, the proportion of problems solved in the minimum number of moves, i.e. perfect solutions, was used. Latency measures were: (a) initial thinking time (planning time), derived by subtracting the time taken to complete the first move of each problem during the control phase from that of the planning phase; and (b) subsequent thinking time per move, derived by subtracting the time to complete the task after the first move during the control phase from that of the planning phase, divided by the number of moves taken for each problem. A total of 135 patients completed this task.

Attentional set-shifting (Owen et al, 1991)

Subjects were required to learn a series of visual discriminations in which one of two stimulus dimensions (shape or line) was relevant. Once correct responding was established, they were introduced to different exemplars of the same dimensions. Subjects needed to maintain attention to the same dimension for correct responding, thus testing their ability to generalise the rule they had just learned (intra-dimensional shift, IDS). At the later, extra-dimensional shift stage (EDS), the rule was reversed so that the previously irrelevant dimension now became relevant. This tested the ability to inhibit the previously correct response set and adopt a new response set by shifting attention from one dimension to the other. Thus, the EDS stage is analogous to the attentional shift involved in Wisconsin Card Sorting Test performance. A total of 133 patients completed this task.

Statistical analysis

Results were analysed using SPSS 10. Latency and DUP data were $\log_{10}$ transformed to reduce skew; *t*-tests were used for two-group single variable measures, with degrees of freedom adjusted according to Levene's test for equality of variance. For repeated measures data, the analysis of variance (ANOVA) was used. To explore whether general IQ explained performance on the more specific tests, Pearson's correlation coefficients between NART IQ and memory and executive variables were calculated and, where significant, the analyses were repeated with an analysis of covariance (ANCOVA) entering IQ as a covariate. For the attentional set-shifting task, the numbers of subjects and controls passing or failing each stage were cast into contingency tables and analysed using the likelihood ratio method (Kullback, 1959; Robbins, 1977). The resultant information statistic (2_i) is distributed as chi-squared. Because of multiple comparisons, α was set at 0.01.

RESULTS

Subjects

Eighty-eight per cent of patients were tested within 8 weeks of recruitment (median 2.7 weeks; range 0–43). Fifty-eight patients were prescribed the newer antipsychotic drugs (42 olanzapine, 15 risperidone, 2 clozapine), 64 patients were prescribed traditional antipsychotic drugs, including sulpiride (24), and 14 patients were drug-naïve. To investigate medication effects, a series of *t*-tests between those receiving traditional and newer antipsychotic drugs were performed on neuropsychological variables and DUP. No differences were evident (range of *t* was 0.08–1.5).

Patients and controls were matched for age but not gender ratio (Table 1). Preliminary analyses were performed on control data and no gender differences in neuropsychological performance were found, in line with previous work with these tests (Robbins *et al*, 1994). The mean IQ of the patient group was significantly lower than that of the control group. The relationship

Table 1 Age, gender and IQ for patients with first-episode schizophrenia and controls

	Schizophrenia (*n*=136)	Controls (*n*=81)	Statistic
Age, years (mean (s.d.))	25.74 (7.99)	26.12 (5.19)	$t(213)=-0.43$, $P=0.67$
Gender: male/female	107/29	49/32	Chi-squared (1)=8.31, $P=0.004$
NART IQ (mean (s.d.))[1]	99.67 (10.37)	104.64 (9.54)	$t(181)=-3.28$, $P=0.001$

NART, National Adult Reading Test.
1. Completed in 110 patients with schizophrenia and 73 controls.

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between IQ and memory and executive function was examined statistically as described above.

Spatial span, pattern and spatial recognition memory

As shown in Table 2, patients were significantly impaired on all three memory tasks. Pattern and spatial recognition memory correlated significantly with IQ (r=0.26 and 0.24, respectively; P<0.001). ANCOVAs showed that, although IQ contributed to performance ($F_{1,177}$=7.17 and 6.38, respectively; P<0.01) the group differences remained significant ($F_{1,177}$=16.19 and 9.65, respectively; P<0.01). Thus, specific impairments in short-term spatial memory capacity and long-term episodic memory were evident in the patient group.

Spatial working memory

Figure 1(a) shows that patients made more errors than controls at the more difficult six- and eight-box stages (group effect: $F_{1,214}$=39.90, P<0.001; group × difficulty interaction: $F_{3,642}$=28.28, P<0.001). IQ correlated with total errors (r=−0.36, P<0.001). An ANCOVA showed that, although IQ contributed to performance ($F_{1,79}$=19.32, P<0.001), the group difference for errors remained highly significant ($F_{1,179}$=16.98, P<0.001).

Performance of this task can be influenced by both short-term memory capacity and the degree to which an efficient strategy is adopted (Owen *et al*, 1990). In our previous study (Hutton *et al*, 1998), spatial span and working memory strategy score correlated with spatial working memory errors in the patient group. Therefore, in the present study, we entered these measures as covariates in separate ANCOVAs. After covarying for strategy, there was no group difference in spatial working memory error score (group effect: $F_{1,213}$=2.05, n.s.), the effect of strategy being highly significant ($F_{1,213}$=138.87, P<0.001). After covarying for spatial span, the group difference for spatial working memory errors remained significant (group effect: $F_{1,212}$=20.17, P<0.001) despite a significant effect of spatial span ($F_{1,212}$=35.82, P<0.001).

Thus, there was a specific impairment in spatial working memory in the patient group. The group difference in errors was largely accounted for by the less efficient use of a search strategy in the patient group rather than differences in short-term spatial memory capacity.

Table 2 Differences between patients with first-episode schizophrenia and controls on CANTAB tests. Values are group mean (s.d.)

	Schizophrenia	Controls	Statistic
Spatial span	5.62	6.58	t(214)=−5.01
	(1.37)	(1.30)	P<0.001
Pattern recognition memory: % correct	84.44	92.81	t(205)=−5.85
	(0.12)	(0.08)	P<0.001
Spatial recognition memory: % correct	67.73	76.47	t(208)=−4.48
	(0.14)	(0.13)	P<0.001
Attentional set-shifting: stage reached	8.37	8.89	t(177)=−4.10
(maximum=9)	(1.33)	(0.45)	P<0.001
Spatial working memory: strategy score	34.96	29.05	t(142)=7.68
	(4.77)	(5.86)	P<0.001

CANTAB, Cambridge Automated Neuropsychological Test Battery.

Planning

Figure 1 shows that patients solved fewer problems perfectly at the 3-, 4- and 5-move levels of difficulty (group effect: $F_{1,213}$=43.01, P<0.001; group × difficulty interaction: $F_{1,639}$=12.51, P<0.001). IQ correlated with perfect solutions (r=0.29, P<0.001). An ANCOVA showed that, although IQ contributed to performance ($F_{1,179}$=6.89, P<0.01), the group difference in perfect solutions remained highly significant ($F_{1,179}$=21.66, P<0.001).

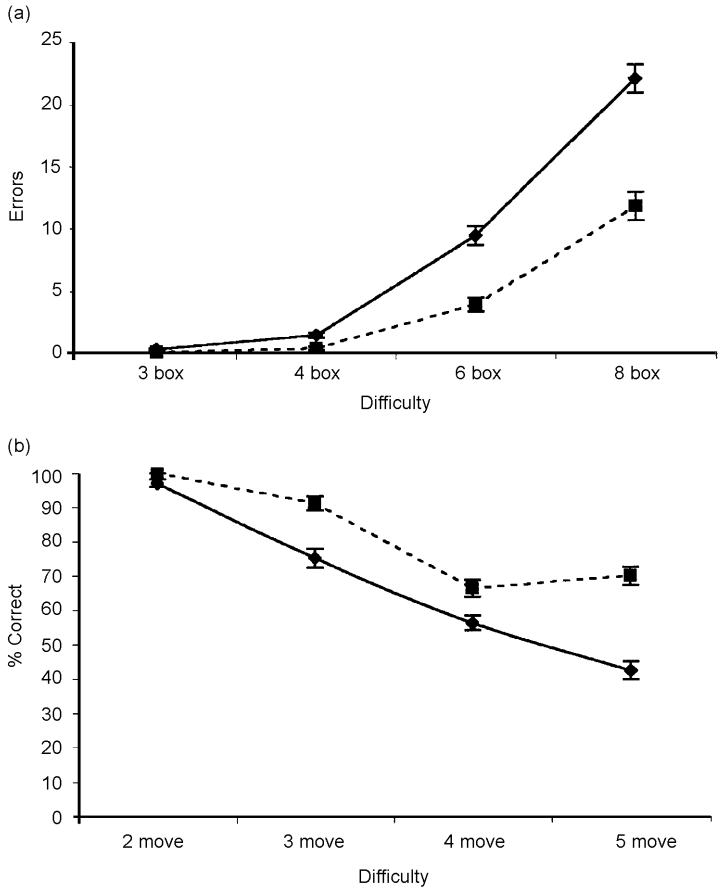

Fig. 1 (a) Spatial working memory errors and (b) percentage of perfect solutions obtained on the Tower of London planning task across varying levels of difficulty in patients with first-episode schizophrenia (◆) and normal controls (■). Error bars represent the s.e.m.

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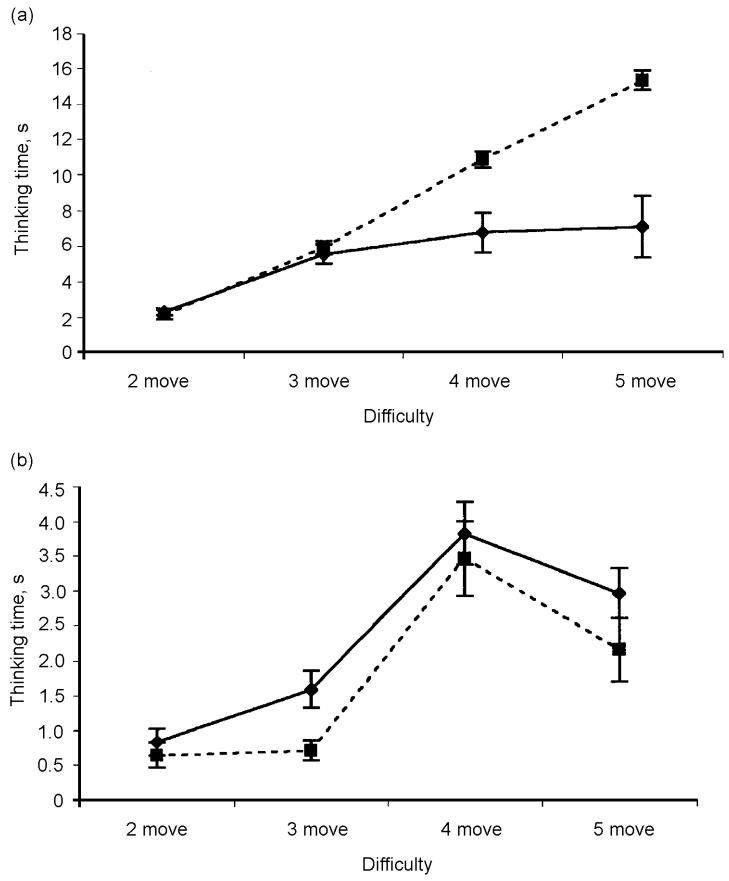

Fig. 2 (a) Initial thinking times and (b) subsequent thinking times across varying levels of difficulty in the Tower of London planning task in patients with schizophrenia (◆) and normal controls (■). Error bars represent the s.e.m.

Figure 2 shows that the time spent thinking about the problem prior to the first move increased linearly with increasing problem difficulty in the control group. This effect was not seen in the patients who were significantly faster (group difference: $F_{1,214}=15.42$, $P<0.001$; group × difficulty interaction: $F_{3,642}=2.95$, $P=0.03$). An ANCOVA showed that IQ did not contribute to initial thinking time ($F_{1,180}=1.87$, n.s.). Patients and controls did not differ in the time taken for each subsequent move ($F_{1,214}=2.83$, n.s.).

Correlations were performed for each group between $\log_{10}$ initial thinking time and proportion of perfect solutions obtained for each stage of difficulty. A highly significant positive relationship was found between time taken to think about the 5-move problem and performance in the control group ($r=0.53$, $P<0.001$) and a weaker, non-significant relationship for the same measures in the patient group ($r=0.16$, $P=0.07$).

Thus, patients were impaired in planning in that they solved fewer moves perfectly. In addition, patients spent significantly less time planning the solutions. Performance was highly related to planning time for the hardest problems in controls but not in patients.

Attentional set-shifting

Figure 3 shows that more patients than controls failed the test. This was significant when measured either by stage reached ($t(177)=-4.11$, $P<0.001$) or by number passing and failing ($2_i=12.26$, $P<0.001$). When the number of subjects passing and failing each stage was examined, this was significant at the extra-dimensional shift stage only ($2_i=7.65$, $P=0.006$). IQ did not correlate with stage reached ($r=-0.09$, n.s.).

As the majority of patients passed the test, we looked for other evidence of impairment in these by examining the number of errors at the intra-dimensional and extra-dimensional shift stages (IDS: patients 1.81 (s.d. 4.94), controls 0.81 (s.d. 0.92); EDS: patients 9.54 (s.d. 9.14), controls 6.13 (s.d. 6.69)). Although there was tendency for patients to make more errors than controls overall (group effect: $F_{1,174}=3.60$, $P=0.06$) they did not make proportionately more errors at the EDS stage (group × stage interaction: $F_{1,174}=0.08$, n.s.). When those passing and failing this task were compared for IQ, spatial span, pattern and spatial recognition memory, spatial working memory errors and perfect solutions on the planning task, there were no significant differences (range of t: 0.26–0.87).

Relationships between neuropsychological function, symptoms and duration of untreated psychosis

Correlations were performed in the patient group between IQ, spatial working memory errors, number of perfect solutions on the planning task, stage reached on the attentional set-shifting task, pattern and spatial recognition memory scores, $\log_{10}$ DUP and scores for positive, negative and disorganisation syndromes (Table 3). The data showed that the neuropsychological scores tended to intercorrelate except for the attentional set-shifting task score, which failed to correlate with any other task. Conversely, only performance on the attentional set-shifting task correlated with $\log_{10}$ DUP ($r=-0.23$, $P=0.01$), indicating that the shorter the duration of untreated psychosis the higher the stage reached. When patients passing and failing this task were compared, $\log_{10}$ DUP was significantly longer in the group that failed (47.5 (s.d. 72.54) weeks *v.* 93.6 (s.d. 118.05) weeks; $t(113)=-2.59$, $P=0.01$).

There were no significant correlations between syndrome scores and neuropsychological scores or $\log_{10}$ DUP (range of $r=0.00$–0.16).

DISCUSSION

This study replicates our original finding that patients with first-episode schizophrenia are impaired on executive tasks of planning and spatial working memory but not attentional set-shifting (Hutton *et al*, 1998). We also found similar impairments in short- and long-term episodic memory.

NART IQ correlated with many measures of memory and executive function,

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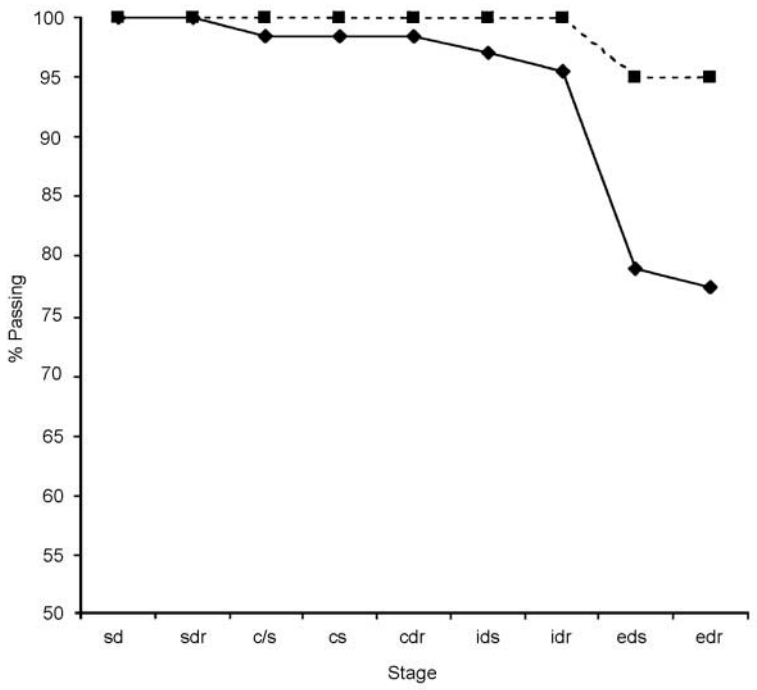

Fig. 3 Percentage of patients passing each stage of the attentional set-shifting task in patients with schizophrenia (◆) and normal volunteers (■). The stages are: sd, simple discrimination; sdr, simple discrimination reversal; c/s and cs, compound discrimination stages; cdr, compound discrimination reversal; ids, intra-dimensional shift; idr, intra-dimensional shift reversal; eds, extra-dimensional shift; edr, extra-dimensional shift reversal.

questioning the specificity of our findings. However, in all cases, significant differences remained between the groups when IQ was taken into account in the statistical analysis. In the patient group, measures of planning, working memory strategy and recognition memory intercorrelated. Neuropsychological performance in the patient group was not related to symptoms or medication type. Taken together, these data suggest that specific impairments in memory and executive function are present at the onset of chizophrenia and that deficits in the two cognitive domains coexist.

Table 3 Pearson correlation coefficients (*r*) for cognitive and clinical measures

	Duration of untreated psychosis (log_{10})	Negative syndrome[1]	Positive syndrome[2]	Disorganisation syndrome[3]
NART IQ	−0.11	0.00	−0.02	−0.02
Attentional set-shifting: stage reached	−0.23*	−0.04	−0.06	0.05
Planning: perfect solutions	−0.11	−0.10	0.10	0.00
Spatial working memory: errors	0.07	−0.03	−0.07	−0.02
Pattern recognition memory: % correct	−0.03	0.14	0.09	−0.01
Spatial recognition memory: % correct	0.02	0.00	−0.02	−0.01
Spatial span	0.13	0.01	−0.07	−0.14
Duration of untreated psychosis (log_{10})		0.11	−0.16†	0.02

SANS, Scales for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; NART, National Adult Reading Test.
1. Derived from sum of global scores for SANS items affective flattening, alogia, avolition, anhedonia.
2. Derived from sum of global scores for SAPS items hallucinations and delusions.
3. Derived from sum of global scores for SAPS items bizarre behaviour and positive formal thought disorder and SANS attention.
*P=0.01; †P=0.07; remaining values not significant.

These conclusions are in agreement with previously published studies (Hoff *et al*, 1992; Saykin *et al*, 1994; Bilder *et al*, 2000).

Nature of executive impairment at the onset of schizophrenia

The analysis of an enlarged cohort of patients and controls and the inclusion of additional neuropsychological and clinical measures allows further interpretation of our results.

The pattern of reduced number of perfect solutions on the planning task and increased spatial working memory errors, because of the inadequate use of a search strategy, is also found in patients with chronic schizophrenia (Elliott *et al*, 1998; Pantelis *et al*, 1999). Patients with frontal lobe resections are similarly impaired but not those with temporal lobe resections or cortical and subcortical dementia such as Alzheimer's disease and Parkinson's disease (Owen *et al*, 1990, 1992, 1995, 1996*c*; Sahgal *et al*, 1992). Functional imaging studies of the planning and spatial working memory tasks in normal volunteers have shown that the critical area of activation is the dorsolateral prefrontal cortex (Baker *et al*, 1996; Owen *et al*, 1996*a*, *b*). Taken together, our results suggest that dorsolateral prefrontal cortex function is impaired at the onset of schizophrenia.

However, the performance of our patients differs from that of patients with chronic schizophrenia and frontal lobe resection in several important respects. In the planning task, our patients were faster to initiate responses than controls but no different in the time taken to complete each subsequent move. Patients with frontal resections and chronic schizophrenia, by contrast, have normal initial thinking times but are slower in thinking about subsequent moves than controls (Owen *et al*, 1990; Pantelis *et al*, 1999).

Another difference between the performance of our patients and that of patients with frontal lobe resection and chronic schizophrenia is with respect to attentional set-shifting task performance. Far fewer first-episode patients failed this task compared with groups of patients with frontal resection (Owen *et al*, 1991) and chronic schizophrenia (Elliott *et al*, 1995; Pantelis *et al*, 1999). Approximately 75% of our patients performed this task normally. They completed the task and made no more errors on the most stringent EDS stage than

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controls. This contrasts markedly with patients with chronic schizophrenia, who are most impaired on the attentional set-shifting task out of all CANTAB executive tasks (Elliott *et al*, 1998).

The minority of patients who did fail the attentional set-shifting task were specifically impaired on the EDS stage, which requires inhibition of a previously acquired response set and a shift of attention away from one stimulus dimension to another. The ability to inhibit a pre-potent response and execute an alternate response is considered a core attribute of prefrontal cortex function and fundamental to performance of other so-called frontal tasks such as the Wisconsin Card Sorting Task. This specific pattern of impairment on the attentional set-shifting task was also found in patients with frontal resections (Owen *et al*, 1991) and performance of the EDS stage critically activated dorsolateral prefrontal cortex in a functional imaging study of normal volunteers (Rogers *et al*, 2000). In patients with chronic schizophrenia, however, failure occurred on EDS and other stages, indicating additional cognitive difficulties in this group such as discrimination learning and rule abstraction (Elliott *et al*, 1995; Pantelis *et al*, 1999).

CLINICAL IMPLICATIONS

- Specific deficits in memory and executive function are present in patients with schizophrenia at illness onset.
- The profile of impairment in executive impairment is different from that of chronic patients and this may be relevant for cognitive rehabilitation strategies at illness onset.
- Pathophysiological processes in prefrontal cortex underlying executive impairment may begin to deteriorate at the onset of psychosis and continue to worsen with time.

LIMITATIONS

- We were unable to distinguish between the effect on cognitive performance of illness duration and delay of antipsychotic drug treatment.
- Duration of untreated psychosis was determined retrospectively.
- IQ was estimated using the National Adult Reading Test, which may better reflect premorbid IQ than current IQ.

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Relationship between neuropsychological function and duration of untreated psychosis

Our findings indicate that at illness onset, the nature of the executive impairment is different from that of chronic patients. The finding that first-episode patients initially respond quicker than controls and the lack of relationship between planning time and correct performance apparent in controls requires further investigation, as this may reflect the involvement of different cognitive processes in the two groups. Further, although there were no relationships between performance and syndrome scores, it would be important to know whether the profile of deficits in first-episode schizophrenia reflects the acute stage of the illness and whether this changes to that of chronic patients over time.

A relationship between chronicity and neuropsychological function is indicated by the finding that the only differentiating factor between those passing and failing the attentional set-shifting task was duration of untreated psychosis. Patients who passed the test had a mean DUP of 47.5 weeks whereas those who failed had been ill for almost twice as long (93.6 weeks). One possible explanation is that prefrontal function begins to deteriorate at the onset of psychosis and thus is more evident in those who had had a longer DUP. In support of this, we found that attentional set-shifting performance had deteriorated at 1-year follow-up assessments in a smaller group of patients (Joyce *et al*, 1999). This would also explain why many more patients with chronic schizophrenia are impaired on this task compared with first-episode patients (Elliott *et al*, 1995; Pantelis *et al*, 1999).

The contribution of duration of untreated psychosis to the severity and outcome of psychosis is controversial (see Verdoux *et al*, 2001). In a previous study we found no association between DUP and symptoms at presentation (Barnes *et al*, 2000). The finding of a robust association between DUP and attentional set-shifting ability in the current study suggests that this task may be more sensitive to the effect of untreated psychosis than symptom measures. However, until longitudinal measures are available, we are unable to distinguish between the effects of illness chronicity *per se* and treatment delay on the pathophysiological processes underlying schizophrenia.

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