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Commentary

Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage

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Abstract

Neuropsychological studies of patients with schizophrenia have consistently identified deficits on tests sensitive to frontal lobe function. One paradigm that has been widely used is that of attentional set-shifting using the Wisconsin Card Sorting Test (WCST). In the present study, patients with chronic schizophrenia and with frontal lobe lesions were assessed on a computerised set-shifting task that provides a componential analysis of the WCST by distinguishing between intra-dimensional and extra-dimensional set-shifting. Out of 51 patients with schizophrenia, those with high IQ ($n=24$) were compared with patients with lesions in prefrontal cortex ($n=22$) and with normal control subjects ($n=18$). These three groups were well matched for age, sex and National Adult Reading Test (NART) IQ. The schizophrenic group showed a significantly higher rate of attrition at the intra-dimensional shift stage of learning compared with the other two groups. At the extra-dimensional shift stage, both the schizophrenic and frontal lesioned groups showed greater attrition than controls. Further, patients with schizophrenia who were able to learn the intra-dimensional reversal stage required more trials and made significantly more errors at that stage than the other two groups. In comparison with high IQ patients with schizophrenia, those with low IQ performed at a lower level but showed a qualitatively similar pattern of performance, providing further evidence that the set-shifting deficits were not simply explained by any global intellectual decline. Patients with schizophrenia who dropped out at the extra-dimensional shift stage had higher negative symptom scores compared with patients dropping out at previous learning stages, while patients failing at the intra-dimensional shift stage had lower scores for bradyphrenia (slowness of thought). The results suggest that patients with chronic schizophrenia fail to 'learn set' and are impaired at both set-shifting and concept formation. The relevance of these findings to understanding the nature of prefrontal cortical deficits in chronic schizophrenia is discussed. The implication of these findings to the rehabilitation of these patients is considered. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Frontal-striatal; IQ; Learning; Neuropsychology; Schizophrenia; Set-shifting; Symptoms

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1. Introduction

Neuropsychological studies of patients with schizophrenia have consistently identified deficits on tests of executive function, traditionally considered sensitive to frontal lobe damage (Kolb and Whishaw, 1983; Stuss et al., 1983) (Taylor and Abrams, 1984, 1987; Weinberger et al., 1986, 1988; Pantelis et al., 1997). Deficits of executive function are characterised by impairments in planning, maintenance of goal-directed behaviour and behavioural flexibility. Tasks employed to assess different aspects of executive function have often used attentional set-shifting paradigms, such as the Wisconsin Card Sorting Test (WCST) (Berg, 1948). In these paradigms, subjects are required to shift attention between different stimulus dimensions on the basis of reinforcing feedback. It is proposed that patients with frontal lesions are impaired in their ability to inhibit previously learned responses and, as a consequence, are unable to shift their attention to the relevant stimulus, thus making errors of perseveration (Milner, 1963).

It has been demonstrated that patients with schizophrenia also perform poorly on tasks of attentional set-shifting (Kolb and Whishaw, 1983; Weinberger et al., 1986; Goldberg et al., 1987; Morice, 1990). In general, the results indicate that patients with schizophrenia achieve fewer sorting categories than controls and display significantly more perseverative errors. The common explanation provided for this performance is that patients with schizophrenia make perseverative errors due to a failure to inhibit inappropriate responses (Pantelis and Brewer, 1996). On the basis of these findings, parallels have been drawn between patients with schizophrenia and those with frontal lobe damage and it has been inferred that set-shifting deficits in patients with schizophrenia are indicative of frontal lobe dysfunction. However, it remains unclear whether patients with schizophrenia fail these tasks because of the same underlying cognitive deficit as frontal lobe patients. One strategy to help elucidate the nature of the deficits in schizophrenia is directly to compare performance with that of other neurological patients (Randolph et al., 1993), as in some recent studies

(Gold et al., 1994; Heaton et al., 1994; Hanes et al., 1996a,b; Pantelis et al., 1997). However, no recent study has directly compared patients with schizophrenia and frontal lesion patients on tests of set-shifting ability.

A second issue arising from studies of set-shifting which use the WCST, is that successful performance requires motivational, attentional, memory, and learning processes, in addition to or instead of intact executive function (Downes et al., 1989). Therefore, similarly poor performances between patients with schizophrenia and patients with specific brain lesions may reflect very different underlying cognitive deficits, as suggested in a positron electron tomography (PET) study comparing patients with schizophrenia and Huntington's disease matched for WCST performance (Goldberg et al., 1990). Recent studies have attempted to separate this complex task into its component cognitive processes. Two types of set-shift have been proposed (Downes et al., 1989): intra-dimensional shifts (IDS), which involve the transfer of a rule within the same stimulus dimension (e.g. choosing circles instead of squares), and extra-dimensional shifts (EDS), which require a transfer of attention across different stimulus dimensions (e.g. choosing on the basis of colour rather than the previous category of shape). In essence, EDS shifting is the core component of the WCST, and is the basis for the achievement of novel sorting categories. IDS shifting is a more basic element of the WCST and is related to the ability of the subject to be aware of the conceptual category within which they are responding. A successful IDS shift requires a generalisation of learning or the ability to 'learn set'. In an attempt to dissect these component processes involved in set-shifting, several recent studies have used a computerised version of the WCST that is graded in complexity, and allows these processes to be separated (Roberts et al., 1987; Downes et al., 1989; Owen et al., 1991).

The present study set out directly to examine set-shifting ability in schizophrenia and to compare this with patients with frontal lobe lesions. Previous studies using the computerised set-shifting task have shown that patients with frontal lobe damage are impaired at the EDS shifting stage

(Owen et al., 1991) and that their responses are perseverative (Owen et al., 1993). Two studies have used a related paradigm to assess patients with schizophrenia (Elliott et al., 1995; Hutton et al., 1998). While Hutton et al. (1998) found that first-episode patients were relatively unimpaired in set-shifting ability, Elliott et al. (1995) demonstrated that patients with established schizophrenia were perseverative, with apparent similarities to the performance observed in patients with frontal lobe lesions. However, as age, education, and IQ vary considerably between psychiatric and neurological patient groups, correct inferences require direct matched comparisons, as in the present study.

The current investigation further set out to address methodological issues in the analysis of set-shifting behaviour. Previous studies using the computerised paradigm have typically analysed the data for attrition rate in a cumulative manner; that is, examining the overall number of patients who had failed the task by a particular stage, as opposed to the actual number who failed at that level. This type of analysis assumes that a patient failing a specific stage will also fail each subsequent stage. Additionally in previous studies, when a subject failed a specific stage they were given the maximum error rate for each subsequent stage, even though they did not attempt them. Also, previous studies have not examined the performance of subjects actually passing any particular stage, in order to assess the level of difficulty encountered by different groups in attaining criterion. These assumptions and data analysis techniques may obscure subtle performance differences between patients who fail at different stages of the test. Importantly, many studies have shown that patients with schizophrenia are not homogeneous in their cognitive deficits (e.g. Seidman, 1990; Shallice et al., 1991; Braff et al., 1991; Anderson et al., 1991). Therefore, it is likely that different patients will fail at different stages and this will reflect different cognitive abnormalities. Previous work has suggested that such variation may reflect the heterogeneous symptomatology which characterises the disorder, and that different patterns of neuropsychological impairment are associated with particular symptom or behavioural profiles

(Liddle, 1987a; Liddle and Morris, 1991; Brewer et al., 1996; Pantelis and Brewer, 1995, 1996; Norman et al., 1997). Therefore, in the present investigation we also investigate the qualitative aspects of performance specifically for those patients who passed at each stage. In this way we were able to examine, first, whether there were subgroups of patients with schizophrenia who could be identified on the basis of their performance on set-shifting; and second, whether these subgroups also differed in terms of their symptomatological and behavioural profile.

2. Method

2.1. Subjects

2.1.1. Patients with schizophrenia

A detailed description of the selection of patients with schizophrenia has been provided elsewhere (Pantelis et al., 1997). Patients were excluded if there was recent drug abuse as assessed with urine drug screening, poor eyesight, history of significant head injury, epilepsy, leucotomy, or other neurological disorder, or significant medical condition considered to affect cognitive performance (including thyroid disease) (detailed in Pantelis et al., 1997). Fifty-one patients (43 males, 8 females) meeting DSM-III-R criteria for schizophrenia (American Psychiatric Association, 1987) participated in the study. The patients were taken from a chronic sample of patients who were inpatients at a long-stay psychiatric hospital on the outskirts of London. The age range was 26–64 years (mean = 48.3, SE = 1.6), mean length of illness was 27.5 years (range: 8–44; SE = 1.4) and the mean length of admission was 18.5 years (range: 1–43; SE = 1.7). At the time of testing, all patients were taking neuroleptic medication. The range of dosage expressed as milligram equivalents of chlorpromazine (CPZEq; Rey et al., 1989; Atkins et al., 1997) was 50–5086 (mean = 1370; SE = 167.6).

Forty-seven of the 51 patients were tested on the National Adult Reading Test (NART) (Nelson, 1982), which provides an estimate of premorbid IQ that is stable over time in patients with chronic schizophrenia (Smith et al., 1998).

Table 1
Subject characteristics

Group		<i>n</i>	Age (SE)	NART IQ (SE)	Sex M:F	Age of onset of illness (SE)	Length of illness (SE)	Length of admission (SE)
Schizophrenia	All	51	48.29 (1.56)	98.15 (2.10)	43:8	20.84 (0.83)	27.45 (1.44)	18.46 (1.66)
	High IQ	24	48.21 (2.15)	108.71 (1.42)	19:5	20.96 (1.33)	27.25 (2.13)	18.20 (2.49)
	Low IQ	23	48.43 (2.56)	87.13 (2.41)	20:3	20.65 (1.12)	27.78 (2.25)	18.63 (2.54)
Frontal Lobe lesion patients		22	44.82 (4.03)	104.81 (2.71)	11:11	-	-	-
Control subjects		18	40.44 (4.03)	110.94 (2.06)	12:6	-	-	-

Patients with schizophrenia scoring less than ten correct words on the NART were further tested using the Schonell Graded Word Reading Test (Schonell, 1942), which provided more accurate assessment at lower IQ levels. The mean estimated IQ (NART IQ) was 98.2 (SE=2.1; range: 65–121). Current IQ of the sample was also assessed in 32 of the patients with schizophrenia using the WAIS-R (Wechsler Adult Intelligence Scale, Revised) (Wechsler, 1981). The scores ranged from 61 to 109 (mean 80.8; SE=2.0) suggesting that there had been significant intellectual decline within the sample, consistent with previous findings in a similar patient group (Nelson et al., 1990).

As the patients with schizophrenia had a low mean IQ in comparison with the frontal lesion patients and normal controls, the 51 patients with schizophrenia were divided into two groups having high and low NART IQ scores. This was achieved using a median split of the NART IQ scores for the 47 patients with schizophrenia for whom these data were available. In order to match patients with schizophrenia and those with frontal lesions effectively, only the 24 patients in the high IQ group (NART IQ score >100) were used for the comparison study. In this group the mean NART IQ score was 108.7 (SE=1.4; range: 100–121) and the mean WAIS-R score was 87.2 (SE=2.3; range: 72–109); all these patients scored above 25 on the Mini Mental State Examination (MMSE) (Folstein et al., 1975). The age range in this subgroup was 26–64 years (mean=48.2, SE=2.2). The 23 (20 male, 3 female) low IQ schizophrenia

patients had a mean NART IQ score of 87.1 (SE=2.4; range: 65–99) and a mean WAIS-R IQ of 73.5 (SE=2.3; range: 61–87). The age range in these patients was 26–64 years (mean=48.4; SE=2.6).

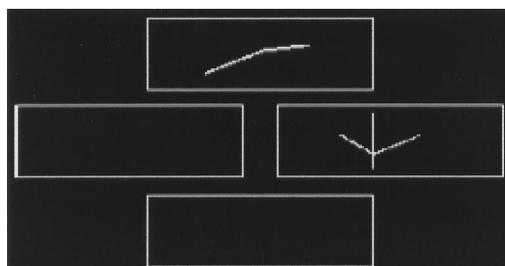
2.1.2. Frontal lobe patients

Data for the patients with frontal lobe lesions ($n=22$) have been described previously (Owen et al., 1990; Pantelis et al., 1997) and are included here for direct comparison. Briefly, these patients had undergone unilateral or bilateral frontal lobe surgery at the Maudsley Hospital Neurosurgical Unit, London. Reasons for surgery included anterior communicating aneurysm clipping, meningioma or other tumour, arterio-venous malformation removal. Patients with computerised tomography (CT) scan evidence of subcortical damage were excluded. The patients were tested, on average, 38 months postoperatively (median=24 months, range: 1–240 months). Fifteen were on anticonvulsant medication at the time of testing.

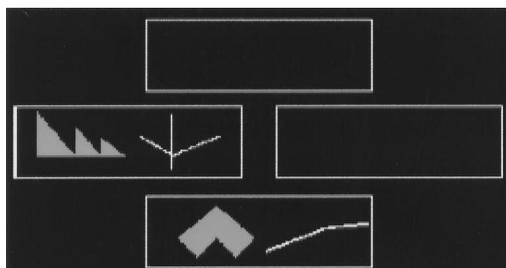
2.1.3. Control subjects

A single group of normal control subjects ($n=18$) was selected to match the two patient groups for age and NART estimated IQ. The control group was selected from a pool of volunteers from the North-East Age Research panel in Newcastle-upon-Tyne.

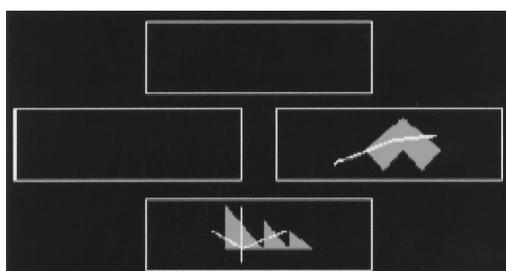
The summary characteristics for the three groups are shown in Table 1. One-way ANOVAs revealed no significant differences between the high IQ schizophrenia patients and the frontal lesion patients or normal controls for sex ($\chi^2=4.33$, $df=$



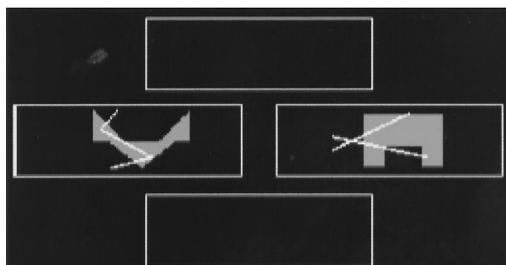
(a)



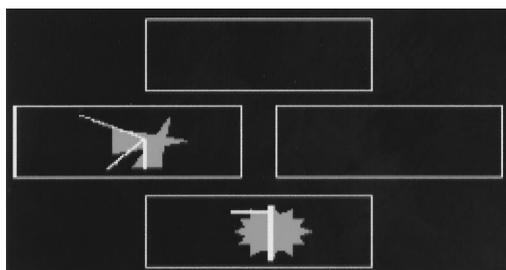
(b)



(c)



(d)



(e)

2, NS), age [$F(2,61)=1.26$, NS], or NART IQ estimates [$F(2,60)=2.08$, NS].

2.2. Procedure

2.2.1. Attentional set-shifting task (ID/ED task)

In this task (Downes et al., 1989; Owen et al., 1991) each subject was required to learn a series of discriminations in which one of two stimulus dimensions (purple-filled shapes or white lines) was relevant and the other was not, using feedback provided automatically by the computer. Four boxes were presented on the computer screen, two of which contained different exemplars of one of the dimensions, either shapes or lines (see Fig. 1). Initially, patients were given a simple simultaneous discrimination (SD) in which subjects had to identify which exemplar was 'correct'. A response resulted in an auditory tone, together with visual feedback which informed the subject if their response was correct; either the word 'CORRECT' in green letters or the word 'WRONG' in red would appear on the screen. The same feedback was used for each of the subsequent stages. After 1.5 s the screen cleared and there was an inter-trial interval of 1 s before the stimuli were again presented but at different locations. Following eight consecutive correct responses the task moved on to the next set-shifting stage.

Following the initial SD stage, the remaining eight stages were as follows. In the second stage (SDR) the previously incorrect choice became the correct one (i.e. the contingencies were reversed). At the third stage (C_D) the second dimension (purple shapes) was introduced with one exemplar of each dimension paired together to form a compound stimulus in two of the response boxes. To succeed, a subject had to continue to respond to the correct exemplar of the previous stage. For this and subsequent stages, exemplars of different dimensions were paired in a pseudo-random fash-

Fig. 1. (a) Simple Discrimination (SD) and Reversal (SDR). (b) Compound Discrimination, with exemplars separated (C_D). (c) Compound Discrimination with overlapping exemplars (CD) and Reversal (CDR). (d) Intradimensional Shift (IDS) and Reversal (IDR). (e) Extradimensional Shift (EDS) and Reversal (EDR).

ion so that all four combinations were used. However, no more than three trials with the same pairings were allowed. The stimuli for the fourth stage (CD) and subsequent stages were also compounds, but the two exemplars from the different dimensions were superimposed, with the white line always in the foreground. The contingencies were again unchanged from the previous two stages. A reversal then occurred at the fifth stage (CDR). New exemplars for both dimensions were introduced at the sixth stage, the intra-dimensional shift (IDS), but the relevant dimension for a correct response was unchanged from stage 1 (i.e. if lines were the correct dimension in stage 1, lines continued to be correct). This was followed by a further reversal at the seventh stage (IDR). In the next stage, the extra-dimensional shift (EDS), new exemplars were again introduced, and subjects were now required to respond to the previously irrelevant dimension (e.g. shapes rather than lines). In the final stage there was again a reversal (EDR) so that response to the previously irrelevant exemplar of the new dimension was required for a correct response. The main measure of performance on this task was the stage successfully attained. Performance indices on the set-shifting task comprised measures of the proportion of patients reaching criterion at each stage, trials to criterion and number of errors at each stage.

2.2.2. Symptom ratings

The Manchester Scale (Krawiecka et al., 1977) was used to assess psychopathology. A new item of 'bradyphrenia' (slowness of thought) was operationally defined (see Appendix A). Psychopathology ratings were made by one of the investigators (TREB), who was trained in using the scale, and who was blind to the neuropsychological assessments.

2.3. Data analysis

2.3.1. Comparison of patients with schizophrenia, frontal patients and healthy controls

In order to match subjects appropriately across the three groups, in this section of the analyses the 23 low IQ patients with schizophrenia were excluded.

2.3.1.1. Attrition rates. Subjects were initially compared in terms of the proportion of subjects in each group reaching criterion at each stage of the test (Fig. 2). The associations between the performance of the different groups were analysed using a likelihood ratio analysis, which is useful with small cell frequencies (Kullback, 1959; Robbins, 1977). The statistic is termed $2i$ and is distributed as chi-square (χ^2).

A separate analysis was performed in order to compare the 'non-cumulative' proportion of each subject group reaching criterion at each learning stage. That is, this analysis compared the actual number of subjects who failed at each individual stage, as opposed to a cumulative score.

2.3.1.2. Trials-to-criterion and number of errors. Further analyses of group differences in performance were undertaken by an examination of the number of trials required to reach criterion at each stage. The groups were compared using a series of one-way ANOVAs, with Bonferroni corrections to minimise Type I error. This analysis was undertaken in two ways: (1) all the subjects who had started the task in each group were included in the comparisons at each stage of learning. For those subjects who did not complete all nine levels due to failure at an earlier stage, the number of trials was inserted as 50. That is, it was assumed that the subject would have failed all subsequent levels and would have used up all 50 of the available trials; (2) only those subjects who reached criterion at that stage were included in the analysis, that is, only those subjects who successfully completed the task within the 50 trials allowed (i.e. this analysis was 'conditional' on passing). This 'conditional' comparison provides a measure of task performance for a subgroup of patients who passed that stage as opposed to examining performance of all subjects regardless of their pass-fail status. The second set of analyses, using only those subjects who passed that learning stage, was conducted in order to determine whether there were qualitative differences between the performance of the three groups when all subjects were passing the test at that level.

The three groups were also compared on the basis of the number of errors produced at each

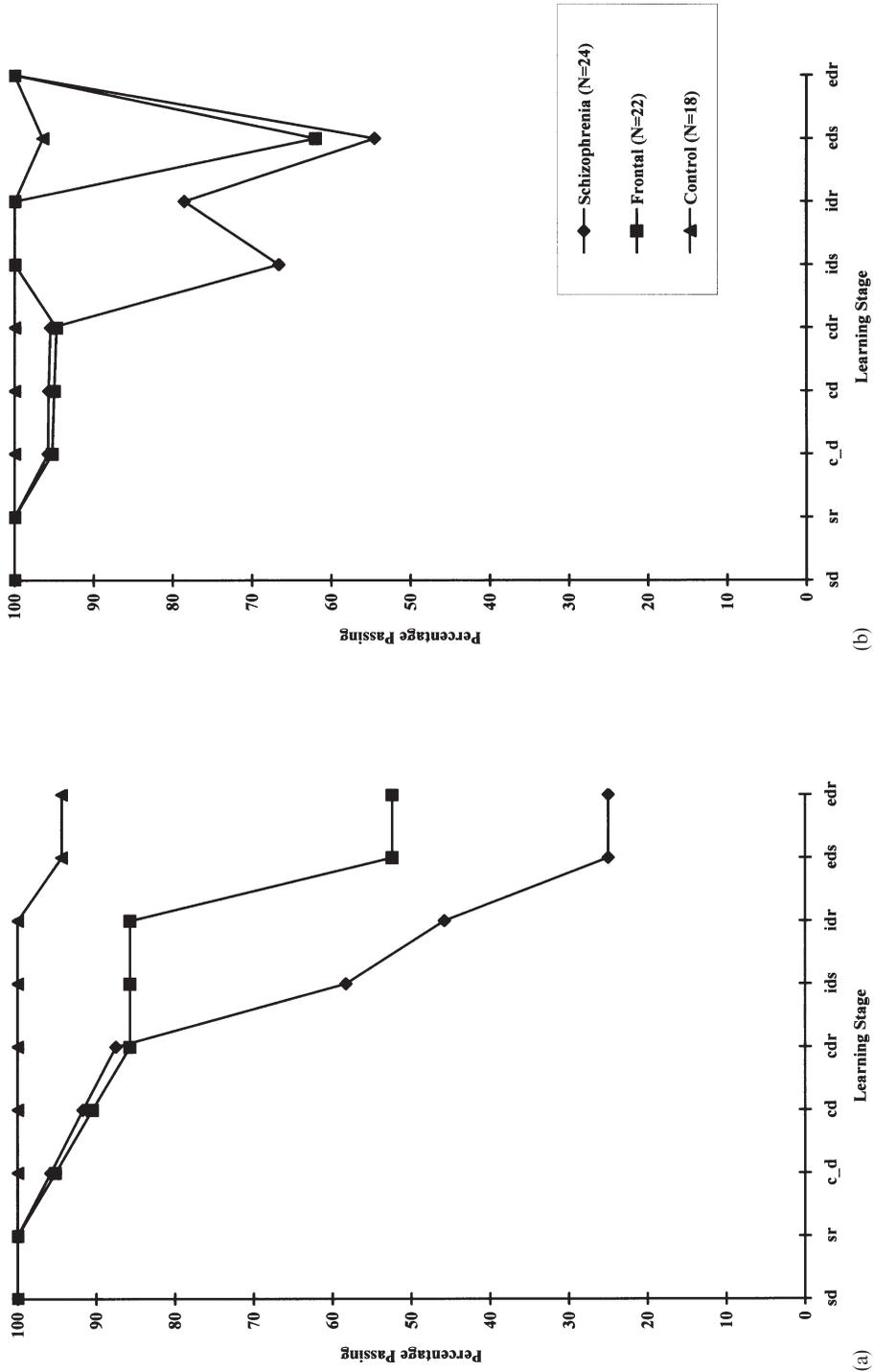


Fig. 2. (a) Percentage of subjects reaching criterion at each learning stage. (b) Non-cumulative attrition rates for each learning stage.

learning stage. In a similar manner to the data for number of trials, a series of one-way ANOVAs was first conducted on the data for all patients regardless of their pass–fail status at that learning stage; a second set of ANOVAs was performed to compare only those subjects passing that learning stage ('conditional' analysis). Again, Bonferroni corrections were applied where appropriate.

2.3.2. Comparison of high and low IQ patients with schizophrenia

The data for this section of the results were analysed in the same way as previously. The one way ANOVAs were performed by comparing the two groups of patients with schizophrenia.

2.3.3. Comparison of symptom rating scale scores with task performance

In order to conduct a more detailed examination of the patients with schizophrenia, all 51 patients were grouped according to their performance on the set-shifting task. Patients were divided into a number of groups, determined by their performance on the set-shifting task (see Results section).

Scores on the Manchester Scale were compared across the groups. In accordance with Liddle's model of three syndromes of schizophrenia (Liddle, 1987b), composite scores for negative, positive and disorganisation syndromes were calculated from the Manchester Scale individual item scores for each patient (Johnstone et al., 1984; Appendix A). A clinical rating of bradyphrenia was examined as a separate item.

The schizophrenia groups were compared with regard to psychopathology using a series of one-way ANOVAs. Where appropriate, *post hoc* Student's *t*-tests were conducted to establish the nature of the differences. Previous investigation of schizophrenic syndrome scores has found an association between negative symptoms and impairment on tests of frontal lobe functioning (Liddle and Morris, 1991). In accordance with these findings, it was proposed that subjects who performed similarly to those with frontal lesions would have more negative symptoms than the other groups. In order to test this hypothesis, a priori contrasts were used in the one-way ANOVA comparing the groups on negative symptomatology.

3. Results

3.1. Comparison of patients with schizophrenia, frontal patients and healthy controls

3.1.1. Attrition rates: cumulative (Fig. 2a)

Significant group differences emerged at the IDS and IDR stages (IDS: $2i=14.32$, $df=2$, $p<0.001$; IDR: $2i=21.07$, $df=2$, $p<0.00005$) and the EDS and EDR stages ($2i=23.15$, $df=2$, $p=0.00001$). Further investigation revealed that the effect was due to an increased number of failures in the patients with schizophrenia, as compared with the other two groups at the IDS and EDS stages (schizophrenia vs controls: IDS: $2i=13.50$, $df=1$, $p<0.0005$; IDR: $2i=18.87$, $df=1$, $p<0.0005$; EDS and EDR: $2i=23.13$, $df=1$, $p<0.0005$), as well as greater failure of the frontal patients in comparison with the control subjects at the EDS stage ($2i=9.61$, $df=1$, $p<0.005$).

3.1.2. Attrition rates: non-cumulative (Fig. 2b)

When examined non-cumulatively, significant group differences were found at the IDS (IDS ($2i=15.729$, $df=2$, $p<0.0005$), IDR ($2i=8.149$, $df=2$, $p<0.05$) and EDS ($2i=8.493$, $df=2$, $p=0.01$) stages. Further analysis comparing each patient group with the normal subjects revealed that, at the intra-dimensional shift stages this was due to a significant attrition of patients with schizophrenia (IDS: $2i=9.97$, $df=1$, $p<0.005$; IDR: $2i=5.36$, $df=1$, $p=0.05$), while there was no attrition in frontal patients or control subjects at these stages. At the EDS stage, both schizophrenic and frontal groups were significantly different to controls (schizophrenia vs controls: $2i=6.69$, $df=1$, $p=0.01$; frontals vs controls: $2i=6.36$, $df=1$, $p=0.01$).

3.1.3. Trials to criterion (Fig. 3a)

Using the first method of analysis, that is including all subjects regardless of whether they had passed or failed, there was a significant main effect of group [MANOVA, $F(2,59)=16.30$, $p<0.00001$], a significant group by shift interaction [Wilks' $\lambda=0.394$, $F(16,104)=3.86$, $p<0.0005$] and a significant main effect of shift [Wilks' $\lambda=0.275$, $F(8,52)=17.10$, $p<0.00001$].

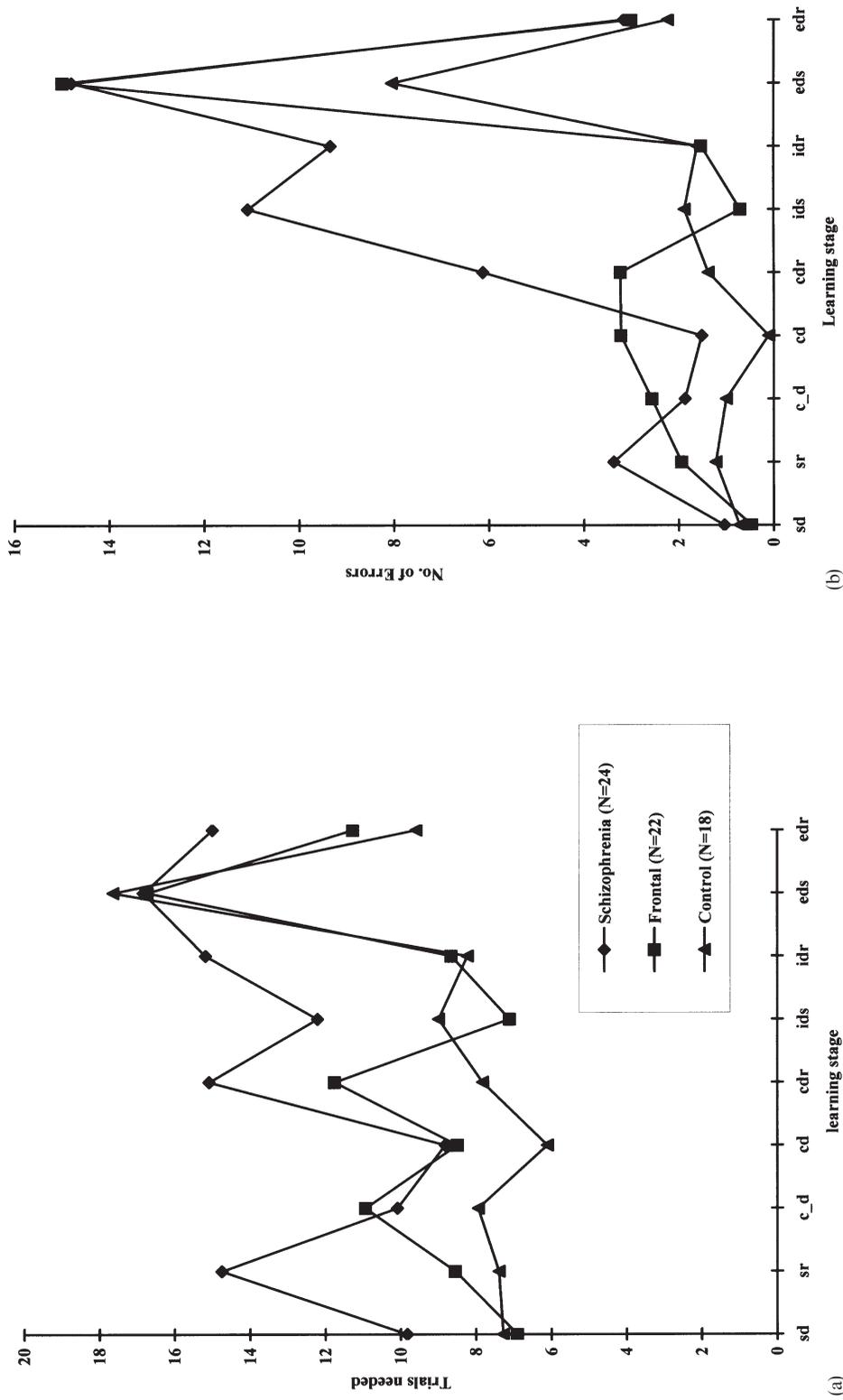


Fig. 3. (a) Trials to criterion for those subjects passing each learning stage. (b) Errors at each learning stage.

Post-hoc tests showed that the schizophrenic group needed significantly more trials to reach criterion than both the other groups at the SD [$F(2,59)=11.31, p<0.0001$], SDR [$F(2,59)=9.86, p<0.0002$], IDS [$F(2,59)=8.05, p<0.001$], EDS [$F(2,59)=9.59, p<0.0002$] and EDR [$F(2,59)=16.40, p<0.00001$] stages. At the EDS stage the patients with frontal lesions were also significantly different from the normal controls and the patients with schizophrenia.

Using the ‘conditional’ method of analysis, only subjects passing the particular stage were examined (Fig. 3a). The patients with schizophrenia needed significantly more trials to reach criterion than both the frontal lesioned patients and controls at the SD learning stage [$F(2,59)=11.31, p<0.0001$], the SDR stage [$F(2,59)=9.86, p<0.0005$] and the IDR stage [$F(2,43)=8.58, p<0.001$]. In addition, the patients with schizophrenia took more trials to reach criterion than the control group but not the frontal group at the CDR stage [$F(2,53)=5.46, p<0.01$].

3.1.4. Number of errors (Fig. 3b)

There was a significant difference in the number of errors produced between the groups at the SDR stage [$F(2,58)=3.94, p<0.05$], IDS stage [$F(2,53)=9.41, p=0.0005$] and at the IDR stage [$F(2,46)=8.84, p=0.001$]. *Post-hoc* tests revealed that this was due to significantly greater errors by the patients with schizophrenia in comparison with the controls at the SDR stage; while patients with schizophrenia made significantly more errors than both the other groups at the IDS and IDR stages. Patients with frontal lesions did not differ from controls for the number of errors.

When errors were analysed for those subjects passing a particular learning stage, significant differences were found at the SDR stage [$F(2,58)=3.94, p<0.05$], which was due to significantly greater errors in the schizophrenic group compared with the normal group. At the IDR stage, patients with schizophrenia passing this stage made significantly more errors than both the frontal lesion patients and the control group [$F(2,43)=5.65, p<0.01$]. There were no differences in error score at the other stages, in particu-

lar, no differences were seen at IDS, EDS or EDR levels of learning.

3.2. Comparison of ‘high’ vs ‘low’ IQ groups

3.2.1. Attrition rate (Fig. 4)

Comparison of the high and low IQ subgroups of patients with schizophrenia revealed a significant difference in cumulative attrition rates only by the EDR stage of learning ($2i=4.34, df=1, p<0.05$). There were no differences in non-cumulative failure rates between the two groups.

3.2.2. Trials to criterion

Analysis of the number of trials to reach criterion between the two groups over all stages of the shift task revealed a significant difference between the two groups [$F(1,45)=5.42, p<0.05$], a significant effect of shift [Wilks’ $\lambda=0.132, F(8,38)=31.30, p<0.0005$] but no group by stage interaction [Wilks’ $\lambda=0.0.790, F(8,38)=1.263, NS$]. *Post-hoc* analysis revealed that there was a significant difference cumulatively at the C_D stage of learning [$F(1,45)=9.38, p<0.005$]. Using the ‘non-cumulative’ method of analysis of trials for each of these groups (i.e. patients failing a particular stage were excluded in the analysis of the subsequent stage), the low IQ group needed more trials to reach criterion at the C_D learning stage compared with the high IQ patients [$F(1,43)=6.55, p=0.01$]. Further, even for those patients passing the C_D stage, the lower IQ group required more trials to reach criterion than the higher IQ group [$F(1,40)=10.29, p<0.005$].

3.2.3. Number of errors

The increased difficulty in performance at the C_D stage was also reflected in a significantly increased number of errors in the low IQ group [$F(1,43)=5.14, p<0.05$]. Analysis of only those patients passing the C_D stage confirmed that the low IQ group produced more errors to reach criterion at that stage [$F(1,40)=10.57, p<0.005$].

3.3. Comparison of symptom rating scale scores with task performance

The above results demonstrated that the patients with schizophrenia showed significant difficulty at

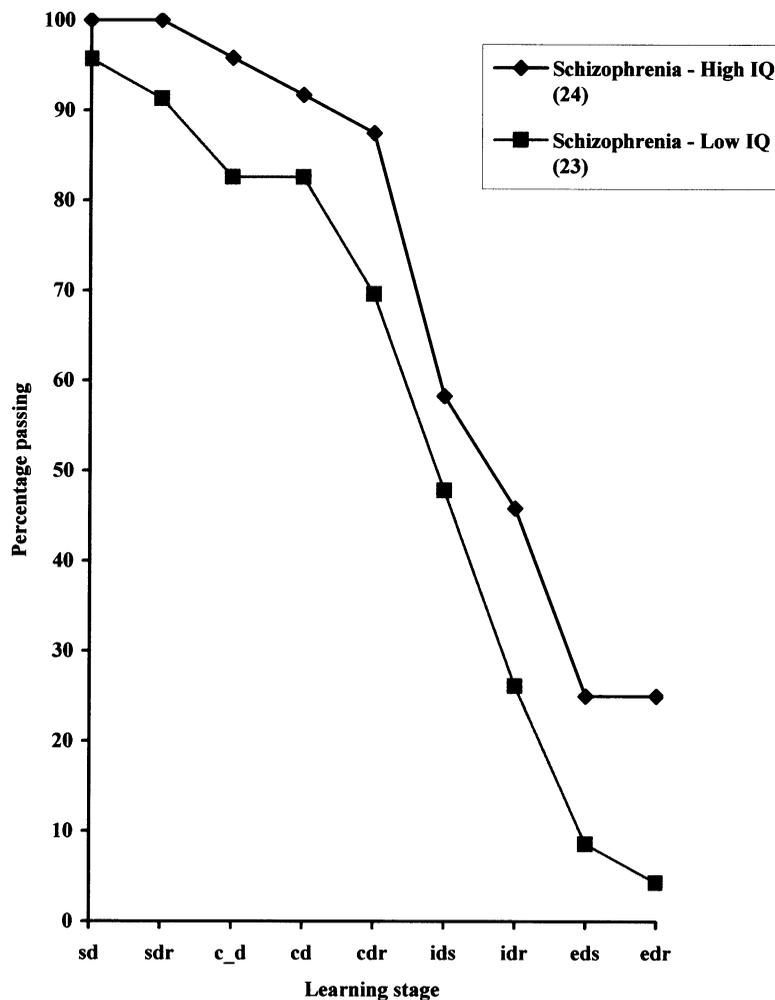


Fig. 4. Set-shifting in 'high' vs 'low' IQ schizophrenia groups.

the IDS, IDR and EDS stages of learning. Patients with schizophrenia were therefore divided into the following groups: (i) those who failed prior to reaching the IDS stage ($n=10$); (ii) those who failed at IDS ($n=13$); (iii) patients failing at IDR ($n=9$); (iv) patients failing at EDS ($n=11$); and (v) those who completed the task ($n=7$). As the group who completed the task had significantly higher NART IQ scores than the other groups [$F(4,42)=4.27$, $p=0.005$], the main comparison examined the first four groups as they did not differ on the IQ measure [$F(3,36)=1.48$, NS]. However, *post-hoc* analysis revealed that the

patients passing all stages did not differ from those failing at IDS or EDS; therefore, the patients failing at these set-shifting stages of the task were compared with those completing the task successfully.

A one-way ANOVA with a priori contrasts showed that patients who failed at EDS had significantly higher negative symptom scores than the other three groups [$t(23.9)=2.80$, $p=0.01$]. Patients failing at EDS also had significantly higher negative symptoms in comparison with those patients passing all stages of the task [$t(16)=2.35$, $p<0.05$]. Comparison of the four groups revealed

that patients failing at the IDS stage had significantly lower scores on the bradyphrenia item [$t(37) = -2.21, p < 0.05$].

3.4. Correlational analyses

For the normal group, there were no significant associations between NART IQ estimates and either errors or trials at any stage of the task. In contrast, the schizophrenic group showed moderate and significant correlations at the C_D ($r_s = -0.40, p < 0.01$) and IDS ($r_s = -0.34, p < 0.05$) stages. The frontal group only showed a significant positive correlation between IDR trials and IQ ($r_s = 0.67, p < 0.05$), indicating that higher NART IQ was associated with a greater number of trials. The normal subjects showed significant correlations between age and performance at the EDS stage of learning ($r_s = 0.52, p < 0.05$). The other groups did not show any correlation with age or NART IQ. Further, for the control subjects, older age was associated with greater number of total errors ($r_s = 0.572, p < 0.05$) summed over all stages, while older age was associated with lower EDID level achieved in the frontal group ($r_s = -0.569, p < 0.01$). In contrast, for the patients with schizophrenia, stage of the task achieved was correlated with NART IQ ($r_s = 0.355, p = 0.01$), which was consistent with the earlier analyses.

In order to examine the influence of illness and treatment factors on performance, correlational analyses were examined for the patients with schizophrenia. Dosage of medication, expressed as milligram equivalents of chlorpromazine, was significantly associated with age ($r_s = -0.545, p < 0.0005$) and illness history (length of illness, $r_s = -0.495, p < 0.0005$; length of current admission, $r_s = -0.409, p < 0.005$; total length of all hospitalisations: $r_s = -0.468, p = 0.001$). These correlations were not significant after covarying for age. Thus, older patients with schizophrenia having longer illness histories were receiving lower doses of medication. There was a trend for patients with negative symptoms to be on lower doses of medication ($r_s = -0.244, p < 0.1$), while there was no relationship between medication dosage and bradyphrenia ($r_s = 0.02, NS$). Higher doses of medication were associated with better performance at

the CD ($r_s = -0.32, p < 0.05$) and EDR ($r_s = -0.29, p < 0.05$) stages of the task. Therefore, the effects of medication do not explain the deficits in performance on the task. Length of illness was associated with poorer performance at the earliest stages (SD: $r_s = 0.28, p < 0.05$; and SDR: $r_s = 0.35, p < 0.05$) of the task, while hospitalisation history was not associated with performance.

With respect to the symptoms of schizophrenia, errors at the SDR stage were associated with greater negative symptoms ($r_s = 0.82, p < 0.05$), while poorer performance at the CD and CDR stages were associated with greater symptoms of disorganisation ($r_s = 0.31$ and 0.30 , respectively, $p < 0.05$). Also, higher scores for bradyphrenia were predictive of poorer performance at the C_D and CDR levels ($r_s = 0.34$ and 0.33 , respectively, $p < 0.05$). No relationship was found between the various performance measures and the positive symptoms of schizophrenia.

4. Discussion

The results of this study, comparing patients with schizophrenia with both frontal lesion patients and matched control subjects, show striking differences in the profiles of the two patient groups on the set-shifting paradigm. While significantly more subjects in both patient groups failed at the extra-dimensional (EDS) stage of the task compared with controls, by far the majority of patients with chronic schizophrenia were unable to reach criterion by the earlier intra-dimensional shift (IDS) and reversal (IDR) stages of learning. Analysis of trial and error data revealed that patients with schizophrenia required more trials to reach criterion than the frontal patients and controls at the simple discrimination and reversal (SD, SDR) and at intra-dimensional (IDS), and extra-dimensional (EDS and EDR) stages of learning. In addition, the patients with schizophrenia produced more errors at the intra-dimensional (IDS and IDR) stages than the other groups. A broadly similar pattern was found when data were analysed excluding subjects who failed that particular learning stage, suggesting that even those schizophrenia patients who were able to achieve criterion at the

IDS stages had significant difficulty in shifting at these levels.

Such differences in performance between patients with schizophrenia and those with frontal lobe lesions would suggest that different underlying cognitive deficits are responsible for task failure. Failure at the intra-dimensional learning stage, and significant difficulty even in those who were successful, indicates a profound impairment in the ability of patients with chronic schizophrenia to generalise a discrimination learned for a particular set of exemplars to another set from the same abstract category. Patients with schizophrenia were able to learn or acquire set, as indicated by their relatively intact performance during the early learning stages, however, the learning of set at the CD stage was not generalised to the IDS when the types of stimuli presented were altered. Thus, these patients were unable to generalise learning which may be due to fundamentally inadequate conceptualisation. This is consistent with other observations in the literature which have suggested that a primary cognitive deficit in schizophrenia is the failure to utilise previously acquired information to influence current perception (Hemsley, 1987, 1994).

Many studies have reported that patients with schizophrenia achieve fewer sorting categories on the WCST than normal controls and some have shown that patients are so impaired at the task that they achieve only one or even no sorting categories. This performance deficit has been attributed to a failure to inhibit the previously relevant sorting category reflected by an increase in perseverative errors (Fey, 1951; Stuss et al., 1983). These deficits have been considered as characteristic of frontal lobe damage and, on the computerised set-shifting task, would show up as a failure to shift attentional set at the extra-dimensional shift stage (i.e. these tasks require shifting between dimensions/categories, rather than evaluating the ability to shift within category). The present results indicate that only a small proportion of these patients with schizophrenia behave similarly to frontal lesion patients and display this 'stuck-in-set' behaviour when attempting the EDS stage. The majority of our patients do not reach the EDS level as they are unable to 'learn set' in the previous stages. Thus,

one explanation for the extremely poor performance of some schizophrenia patients on the WCST is that they have failed to grasp the most basic conceptual requirements of the task. This view is supported by some of the recent literature regarding training patients with schizophrenia on the WCST. Many authors have found that patients' performance does not improve on the test following instruction (Goldberg et al., 1987; Stuss et al., 1983; Schneider and Asarnow, 1987).

The present results indicate that while set-shifting tasks, like the WCST, are useful in assessing the ability to make extra-dimensional shifts they may be less appropriate as a measure of set-shifting ability in patients with schizophrenia who have a more general difficulty in establishing set. If patients are unable to attain even one sorting category the task becomes merely a binary discrimination between those who can grasp the requirements of the sorting test and those who cannot, rather than a detailed description of set-shifting behaviour. Thus, failure on the WCST may not be due to a specific deficit in inhibiting previous experience but may in some patients be attributable to a fundamental impairment in concept formation.

Elliott et al. (1995) used a modified version of the set-shifting task to test a sample of younger, community-based patients with schizophrenia. By contrast to the present study, they found that the greatest attrition rate was at the EDS stage, with very few patients failing at the intra-dimensional shift. Additionally, the schizophrenia patients in their study showed 'stuck in set' behaviour similar to that shown by frontal lesion patients on the same task (Owen et al., 1993). The discrepant results may be accounted for by differences in the overall severity and chronicity of illness between the two samples. The patients with schizophrenia used in the current study had been hospitalised for an average of 18 years and, as such, represent a severely disabled sample. This extreme chronicity of illness is likely to be reflected in the clinical presentation of the samples; although Elliott and colleagues do not report symptom data in their patients, the results from the present study indicate that symptomatological differences are associated

with variations in performance on the set-shifting task (see below).

Severity and chronicity of illness may impact on task performance in two ways. First, it may be presumed that patients who become chronic are, by definition, more severely affected by schizophrenia *from the outset* and therefore would always have performed more poorly on the set-shifting task. As such, impaired performance at early stages of the illness would be predictive of a more chronic course. With reference to the present study this would imply that the patients would always have shown impairment at the intra-dimensional shift level. Second, chronicity of illness may relate to the number of neural systems that have been progressively compromised by the disease process. Successful completion of the set-shifting task requires a number of different executive and memory processes (for example: attention, inhibition, response selection), which need to work interactively for the task to be completed successfully and may each be subserved by separate neural systems, as discussed elsewhere (Pantelis and Brewer, 1995, 1996). Thus, while Elliott et al. (1995) found a discrete executive impairment, the present study discovered a more severe and generalised cognitive deficit, perhaps reflecting the larger number of neural systems that have been compromised. This was also suggested by the profound deficits observed on a range of other tasks of executive function shown by patients derived from the same cohort as the present study (Pantelis et al., 1997). In our patient group, there was no relationship found between set-shifting ability and length of hospitalisation, age, illness duration or period of hospitalisation. Interestingly, in a first-episode study by Hutton et al. (1998), patients had relatively preserved performance on a similar set-shifting task, while there was some evidence for deterioration on this task after 12 months (Joyce et al., 1998). Longitudinal studies of this kind over longer periods are necessary adequately to examine the relationship of neurocognitive deficits to illness chronicity.

While there is debate about the presence of specific neuropsychological impairments that are not explained by a generalised cognitive decline (Nelson et al., 1990; Barber et al., 1996), the

results of our study indicate that the set-shifting deficit cannot be explained in this way. Thus, patients and controls were matched for NART IQ, and MMSE scores for the matched patients with schizophrenia were within the normal range. Further, lower IQ subjects with schizophrenia performed in a qualitatively similar manner to the higher IQ patients. As seen in Fig. 4 the performance of patients with high IQ scores is shifted to the right indicating superior overall performance although the profile of attrition between these two IQ groups was similar. These data are in accord with the findings of a recent study in which a small sample of schizophrenia patients with 'preserved' intellectual function were found to have specific deficits on a version of the ID/ED set-shifting task (Elliott et al., 1998).

The performance profile of the patients with schizophrenia reveals a gradual rate of attrition across the nine learning stages, as well as the sudden attrition observed at intra- and extra-dimensional stages. Previous research using this computerised set-shift paradigm has shown that neurological patients, with frontal damage or disorders of the basal ganglia (including Parkinson's disease and multi-system atrophy), as well as younger patients with schizophrenia and those with unipolar depression drop out substantially at the extra-dimensional learning stage, but there is very little subject attrition at the IDS stage (Downes et al., 1989; Owen et al., 1992; Elliott et al., 1995; Robbins et al., 1994; Purcell et al., 1997). In addition, Parkinsonian and frontal lesion patients who were able to achieve a particular shift were consistently able to pass the reversal form of this shift. In the present investigation, many patients with schizophrenia were unable to complete the intra-dimensional reversal shift (IDR) despite having successfully achieved criterion at the preceding IDS stage. This was not observed at extra-dimensional reversal shift (EDR), which was passed by all those patients who successfully completed EDS. A possible explanation for this failure at IDR may be that those patients who passed at IDS but went on to fail at IDR did not achieve a 'true' intra-dimensional shift and therefore were unable to manipulate the newly learned rule in order to succeed at the reversal level. This explana-

tion is supported by the data showing that the number of errors at IDS was significantly higher for patients with schizophrenia who passed the IDS stage than for the normal controls and frontal lesion subjects, suggesting that patients with schizophrenia had some difficulty in fully understanding the new rule.

An alternative explanation for the failure of patients to achieve criterion at IDR is that there is a specific difficulty for these patients in undertaking a reversal shift. The data for trials and error scores revealed that patients with schizophrenia had difficulty at the SDR stage and that both the schizophrenia and the frontal group committed more errors at CDR than the normal controls. This result is consistent with that found by Elliott et al. (1995) who also found an increased number of errors produced at the SDR stage by comparison with SD.

Specific impairments of this kind, in the ability to perform an intra-dimensional shift have not been identified in other groups of patients, except in the advanced stages of some dementing illnesses. Patients early on in the course of Huntington's disease (HD) and Alzheimer's disease generally do not demonstrate such an impairment at the IDS stage. However, later in the course of these conditions, patients are unable to perform the earlier stages of the task, although this is in the context of more generalised neuropathological changes and a range of other neuropsychological deficits (Sahakian et al., 1990; Lange et al., 1995; Lawrence et al., 1996). The comparison with HD is more relevant here, as the studies indicate a progression of impairment in set-shifting ability, with a profound deficit in extra-dimensional shifting during the early stages, but with dramatic increases in perseveration during the reversal phases of the task in more severe forms of the illness (Lange et al., 1995; Lawrence et al., 1996). Lawrence et al. (1996) have argued that this is consistent with current understanding of neuropathological progression in the caudate of HD patients and for involvement of the dorso-lateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) and their caudate connections, with the latter (i.e. OFC) being implicated later in the history of the illness as the more ventral caudate areas become

involved. It is apparent from our study that, while the most severe deficits occur at the intra- and extra-dimensional shift stages, there are also difficulties in reversal learning. Dias et al. (1996a), in their study of marmosets showed that set-shifting, specifically extra-dimensional shift, was associated with lesions of the DLPFC, while failures in reversal learning occurred after lesions of the orbitofrontal cortex. Recent findings of greater deficits on reversal stages of the ID/ED paradigm in those frontotemporal dementia patients having more selective OFC involvement also support these conclusions (Rahman et al., 1998). This would suggest the possible involvement of these areas and their basal ganglia connections in schizophrenia. While there is good evidence for involvement of DLPFC in schizophrenia (Weinberger et al., 1986), few studies have specifically addressed OFC function though there is increasing evidence for its involvement (e.g., Brewer et al., 1996).

From the results of the present study, it might be predicted that an inability to generalise a rule from one situation to another similar, yet altered setting, would impair patients' ability to generalise what they had learned. Thus, skills learned in one setting, such as a ward, may not necessarily be carried into a community setting. This suggests that rehabilitation interventions would benefit by evaluating the presence and severity of such deficits in their patients and developing appropriate strategies for remediation, as has been undertaken in a few recent studies (Green et al., 1990, 1992; Delahunty et al., 1993; Morice and Delahunty, 1996).

4.1. Relationship of set-shifting ability to the symptoms of schizophrenia

There was a strong correlation between negative symptoms and performance at the SDR learning stage, indicating that greater severity of negative symptoms in schizophrenia was predictive of poorer performance at the earliest stages of the set-shifting task. This suggests that patients with prominent negative symptoms were more likely to have difficulty in understanding the requirements of the set-shifting task. Alternatively, the amotiva-

tion and apathy associated with these symptoms may influence their ability to participate.

In terms of the symptomatological differences between patients failing at different learning stages, patients who failed at EDS had higher levels of negative symptomatology, which are characteristic symptoms of chronically hospitalised patients, such as those in the present study (Nelson et al., 1990). Further, those schizophrenia patients who performed more like the frontal lesion patients were characterised by the presence of negative symptoms, including flat affect and poverty of speech. This finding is consistent with previously reported associations between the negative symptoms of schizophrenia and performance on tests sensitive to frontal lobe lesions, such as the WCST (Addington et al., 1991; Liddle, 1987a; Liddle and Morris, 1991; Brown and White, 1992; Norman et al., 1997; Berman et al., 1997; for discussion, see Pantelis et al., 1992; Elliott and Sahakian, 1995). It should be noted that few previous studies have specifically investigated the relationship between neuropsychological domains and symptom-based syndromes using a priori hypothesis testing. In the studies by Norman et al. (1997) and Berman et al. (1997) the negative symptoms (psychomotor poverty syndrome) were associated with WCST performance, which is consistent with our findings of a relationship between impaired extra-dimensional set-shifting and negative symptoms. It is relevant here that deficits in the ability to shift attentional set to previously irrelevant stimuli (extra-dimensional shifting) have been associated with abnormalities of the dorso-lateral prefrontal cortex (DLPFC) (Weinberger et al., 1986) (Pantelis and Brewer, 1995, 1996; Dias et al., 1996a,b) and the negative symptoms of schizophrenia have been linked to hypofrontality of this region (e.g. Liddle et al., 1992; Rodriguez et al., 1997).

In the present investigation, patients who failed at IDS had lower scores on the clinical measure of bradyphrenia than those failing at other stages of the task, indicating that these patients were faster. Given that they failed at this relatively simple level of the task, it is likely that they acted quickly but inaccurately. This suggests that they were not paying sufficient attention to the task

contingencies. Rather, they acted impulsively (as also observed on Tower of London tasks—Pantelis et al., 1997; Hutton et al., 1998) and/or were unable to inhibit their inappropriate responses. This would also be consistent with the observed association between poor performance just prior to the IDS stage and high scores for the disorganisation syndrome. Patients with the latter symptoms have been characterised as showing greater intrusions of inappropriate cognitions or of inappropriate behaviours (McGrath, 1991). Deficits of impulse control and the inability to inhibit inappropriate responses have been linked to lesions in orbitofrontal areas (for discussion: Pantelis and Brewer, 1995, 1996).

Thus, in the present study significant differences in set-shifting performance were associated with specific symptomatological profiles, which may implicate different underlying neural systems, as has been previously suggested (Liddle, 1987a; Liddle and Morris, 1991; Liddle et al., 1992; Norman et al., 1997).

4.2. *Conclusions*

The present results indicate that there is a subgroup of patients with significant negative symptoms who exhibit some similar performance deficits to patients with frontal lesions, namely, failure to perform an extra-dimensional shift. However, the major deficit observed in this chronically hospitalised group of patients occurs at an earlier set-shifting stage, which requires an intra-dimensional shift. This reflects a failure to 'learn set' and to generalise what was previously learned when novel material is presented, even when the rule remains unchanged. Further, failure at this stage was associated with a tendency to act quickly in an impulsive manner, suggesting a failure of appropriate inhibitory mechanisms to monitor performance. Poor performance at the early stages of the task was also associated with the symptoms of the disorganisation syndrome, which has been linked to failure of inhibitory mechanisms. This differential pattern of performance and of relationships to the different syndromes of schizophrenia supports the notion of separate underlying pathophysiological mechanisms, involving separate fron-

tal-striatal systems (Robbins, 1990; Pantelis and Brewer, 1996).

Further, such failures of learning and the inability to apply learning to similar but novel situations has profound implications for the rehabilitation of these patients. The results suggest that rehabilitation strategies for patients with chronic schizophrenia should be introduced in those settings to which patients will be discharged, as they are unlikely to be able to generalise what was learned prior to discharge.

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Appendix A

A.1. Manchester Scale (Krawiecka et al., 1977)

This scale rates a number of reported and observed items and includes measures of positive and negative symptoms of schizophrenia. The scale was modified by separating the items of flattening of affect and incongruity of affect (Johnstone et al., 1984). Furthermore, a new item of 'bradyphrenia' was operationally defined, as set out below. *Bradyphrenia* refers to a slowness of thought assessed on the basis of slowness and hesitation of speech, and a delay in replying to questions at clinical interview. Ratings from '0' to '4' were made as follows:

(1) *Rating '0', Absent*—Normal manner and

speech during interview. Questions answered fairly promptly; air of spontaneity when responding to questions.

- (2) *Rating '1', Mild*—Although there may be evidence of slowness or poor spontaneity, the rater considers that this is either a HABITUAL TRAIT or that it does NOT amount to clearly pathological proportions.
- (3) *Rating '2', Moderate*—The rater detects slowness, or lack of spontaneity at interview and attributes this to psychiatric illness; it is JUST CLINICALLY DETECTABLE. Delays in answering questions would merit this rating provided that the rater considers it is part of a morbid mental state rather than a habitual trait of the patient.
- (4) *Rating '3', Marked*—Slowed thinking attributable to psychiatric illness is EASILY detectable at interview and is thought to make a material contribution to the abnormalities of the patient's present mental state. OR, There may be a long delay before the patient begins to respond to questions, and/or the replies may be slow and drawn out.
- (5) *Rating '4', Severe*—Bradyphrenia is present in extreme degree.

These ratings were used to generate syndrome scores, as follows: (a) negative syndrome score was the sum of scores for 'poverty of speech' and 'flattening of affect'; (b) positive syndrome score was the sum of scores for 'delusions' and 'hallucinations'; (c) disorganisation syndrome score was the sum of scores for 'incoherence of speech' and 'incongruity of affect'.

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