Executive and mnemonic functions in early Huntington’s disease

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Summary
Eighteen patients with early Huntington’s disease were compared with age- and IQ-matched control volunteers on tests of executive and mnemonic function taken from the Cambridge Neuropsychological Test Automated Battery. Tests of pattern and spatial recognition memory, spatial span, spatial working memory, spatial planning and visual discrimination learning/attentional set shifting were employed. These tests have previously been found to be sensitive to the later stages of Huntington’s disease. Patients with early Huntington’s disease were found to have a wide range of cognitive impairments encompassing both visuo-spatial memory and executive functions, a pattern distinct from those seen in other basal ganglia disorders. In contrast to patients with more advanced Huntington’s disease, early Huntington’s disease patients were not impaired at simple reversal learning, but were impaired at performing an extradimensional shift (EDS). The results will be discussed in relation to the hypothesized neuropathological staging of Huntington’s disease and to the anatomical connectivity of the striatum.

Keywords: Huntington’s disease; striatum; subcortical dementia; executive functions; memory

Abbreviation: EDS = extradimensional shift

Introduction
Huntington’s disease is characterized clinically by a triad of progressive motor, psychiatric and cognitive symptoms and neuropathologically by the loss of GABA-containing medium-size spiny neurons in the neostriatum (Folstein, 1989). Since the primary pathology in Huntington’s disease lies within subcortical regions of the brain, Huntington’s disease has been characterized as a ‘subcortical’ dementia, in contrast with the ‘cortical’ dementia of Alzheimer type where the primary site of pathology lies in cortical regions (Albert et al., 1974). The cardinal features of ‘subcortical’ dementias are considered to be problems in retrieving memories, slowed information processing, cognitive inflexibility and mood and personality changes, in contrast to the aphasia, agnosia and amnesia of dementia of Alzheimer type (Cummings, 1990). It has been noted by many investigators that the cognitive disturbances seen in ‘subcortical dementia’ resemble those seen following lesions of the prefrontal cortex (Cummings, 1993). In order to explain these findings, recourse has been made to recent anatomical evidence for the existence of a series of five parallel and (at least partially) segregated circuits, each of which leads from a discrete frontal region, via separate areas of the basal ganglia and thalamus, back to the frontal region from which it originates (Alexander et al., 1986; Parent and Hazrati, 1995). In the light of these findings one might well expect the cognitive symptoms of Huntington’s disease to be similar to those seen following focal lesions to the prefrontal cortex and if so, the term ‘fronto-striatal’ dementia (Robbins et al., 1994) might be more appropriate for Huntington’s disease.

Lesions of the prefrontal cortex result in impairments in ‘executive’ functions. The term executive function refers to a variety of cognitive activities considered to be at the pinnacle of human cognition, e.g. planning and decision-making. These are functions which rely upon, but cannot be reduced to, other cognitive faculties, such as memory and perception (Tranel et al., 1994). Several investigators have
claimed that patients with Huntington's disease show an executive impairment as they perform poorly on tasks such as the Wisconsin Card Sorting Test (Josiassen et al., 1983), the Stroop task (Swerdlow et al., 1995), verbal fluency (Rosser and Hodges, 1994) and Tower of Hanoi-style problems (Saint-Cyr et al., 1988; but see Butters et al., 1985), tasks which are all sensitive to prefrontal cortical lesions (Tranel et al., 1994).

In a recent study, the performance of patients with Huntington's disease relatively late in the course of the disease and patients with dementia of the Alzheimer type, matched for degree of dementia has been examined by us on tasks of executive and mnemonic function (Lange et al., 1995). In keeping with the proposed distinction between fronto-striatal and cortical dementias, the patients with Huntington's disease were significantly more impaired than patients with dementia of Alzheimer type on tasks of executive function which have been shown previously to be impaired by focal lesions to the prefrontal cortex (for review, see Robbins et al., 1996). These included the Tower of London test of planning, a self-ordered spatial working memory task and an attentional set shifting paradigm which deconstructs the Wisconsin Card Sorting Test into its constituent elements. The former two of these tasks have been shown to activate distinct regions of the prefrontal and parietal cortices using PET (Baker et al., 1996; Owen et al., 1996). Performance on the spatial working memory task and the Tower of London is quite highly correlated (Owen et al., 1992), suggesting that spatial working memory is an important component of planning ability. Additional tests were also administered in the investigation of late Huntington's disease patients by Lange et al. (1995), further to specify the nature of possible contributory spatial memory impairments to impaired executive functions. These included a test of spatial recognition memory, sensitive to frontal lobe lesions (Owen et al., 1995) and a test of spatial span, which although insensitive to frontal lobe damage (Owen et al., 1995), activates a region of ventral prefrontal cortex (area 47) as well as a region of parietal cortex (Owen et al., 1996).

In the Lange et al. (1995) study, patients with Huntington's disease also showed a greater impairment than patients with dementia of Alzheimer type on a test of pattern recognition memory, sensitive to temporal lobe lesions and amygdao-hippocampectomy but not to frontal lobe lesions (Owen et al., 1995). This result suggests that not all the cognitive deficits of Huntington's disease can be explained by a 'fronto-striatal' hypothesis. However, the Huntington's disease patients were in the advanced stages of the disease, where rather widespread cortical atrophy is known to occur (e.g. Mann et al., 1993) and it is likely that differences between the dementias will be at their greatest in the earlier stages of disease, when pathological changes are relatively restricted. Thus, in order to test the fronto-striatal hypothesis more clearly we examined the performance, on the same test battery, of patients in the relatively early stages of Huntington's disease where damage is thought to be restricted primarily to the caudate nucleus and putamen (Vonsattel et al., 1985). In addition, although there have been a small number of studies of the progression of cognitive decline in Huntington's disease (e.g. Moses et al., 1981; Josiassen et al., 1983; Bamford et al., 1995), there is still relatively little knowledge about the exact staging of executive function impairments in Huntington's disease. A cross-sectional comparison with the data of Lange et al. (1995) allowed us to examine this issue in detail.

Methods
Subjects
Patient group
Eighteen out-patients with symptomatic Huntington's disease (Huntington's disease), six women and 12 men, mean age 44.1 years (SD 12.2 years), took part in this study. Care was taken to select patients early in the course of the disease. Eight of the patients attended the Department of Clinical Neurology at the National Hospital, London and were diagnosed on the basis of clinical signs and a positive family history (Folstein et al., 1986). The remaining 10 patients attended the Huntington's disease clinic at the Department of Clinical Genetics, Addenbrooke's Hospital, Cambridge and had tested positive for the abnormal expansion of the huntingtin gene (Huntington's Disease Collaborative Research Group, 1993; Warner et al., 1993).

The mean age at onset for the group as a whole was 40.1 years (SD 10.7 years) and the mean duration of chorea was 4.0 years (SD 2.3). Three patients were receiving medication at time of testing. One patient was receiving diazepam (2 mg per day), one sulpiride (50 mg per day) and one temazepam and haloperidol (3 mg twice daily). Two of the Huntington's disease patients were suffering from depression at the time of testing.

The eight London patients were administered the chorea scale of the Quantified Neurological Examination (David et al., 1987). This scale ranges from 0 to 25 (a high score denoting severe impairment) and the patient group scored a mean of 6.1 (SD 1.4). It is likely that differences between the dementias will be at their greatest in the earlier stages of disease, when pathological changes are relatively restricted. Thus, in order to test the fronto-striatal hypothesis more clearly we examined the performance, on the same test battery, of patients in the relatively early stages of Huntington's disease where damage is thought to be restricted primarily to the caudate nucleus and putamen (Vonsattel et al., 1985). In addition, although there have been a small number of studies of the progression of cognitive decline in Huntington's disease (e.g. Moses et al., 1981; Josiassen et al., 1983; Bamford et al., 1995), there is still relatively little knowledge about the exact staging of executive function impairments in Huntington's disease. A cross-sectional comparison with the data of Lange et al. (1995) allowed us to examine this issue in detail.

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The 10 Cambridge patients were administered the functional assessment scale of the unified Huntington's disease rating scale (Huntington Study Group, 1996). This is a 25-item scale designed to assess functional impairment in Huntington's disease, a score of 25 indicating no impairment in activities of daily living and 0 representing maximal impairment. The patients' mean score was 21.9 (SD 3.1), indicating very mild disability. In addition, the Cambridge group were administered the Mini-Mental State Examination (Folstein et al., 1975), a validated measure of dementia, scoring a mean of 28.0 (SD 1.3) out of a possible maximum of 30. None of the patients scored below the cut-off score
for dementia of 24. Unfortunately, the London group were not administered an activities of daily living scale. However, functional capacity correlates highly with scores on dementia rating scales (Folstein, 1989, p. 36) and none were considered to be more than mildly functionally impaired. CT scans were not available for either group.

A one-way ANOVA revealed that the London group were significantly younger than the Cambridge group \(F(1,16) = 5.40, P = 0.03\). The mean age of the London group was 37.4 years (SD = 9.1 years) compared with 49.4 years (SD 12.1 years) for the Cambridge group. Further analyses, using age as a covariate, revealed that the two patient groups did not differ significantly on any of the cognitive measures.

**Control subjects**

Eighteen control subjects were chosen to match the patient group as closely as possible with respect to both age and premorbid verbal IQ as measured by the National Adult Reading Test (Nelson, 1982). These subjects were drawn from a pool of control volunteers recruited through advertisements placed in the Cambridge employment centre. Unpaired \(t\) tests revealed that the two groups did not differ in terms of age \(t(34) = 0.45, P > 0.6\] or estimated premorbid verbal IQ \(t(34) = 0.35, P > 0.7\).

For the visual discrimination learning and attentional set shifting task, the patient group was compared with a separate group of control volunteers \(n = 30;\) mean age = 42.4 years (SD = 19.9); mean National Adult Reading Test = 114.7 (SD = 7.5) drawn from the North East Age Research panel in Newcastle upon Tyne and from the Newcastle, Cambridgeshire and London areas. This group did not differ significantly from the Huntington's disease patients in age \(t(46) = 0.32, P = 0.8\] or National Adult Reading Test scores \(t(46) = 1.2, P = 0.2\].

A summary of the characteristics of the three groups is presented in Table 1. Informed consent was obtained from all patients and control volunteers.

**Table 1 Group characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (years)</th>
<th>NART</th>
<th>Onset</th>
<th>Duration</th>
<th>MMSE</th>
<th>KOLT</th>
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<tr>
<td>CS</td>
<td>18</td>
<td>41.9 (8.5)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>CS2</td>
<td>30</td>
<td>42.4 (7.5)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Data shown are mean (SD) values; NART = National Adult Reading Test (Nelson, 1982); MMSE = Mini-Mental State Examination (Folstein et al., 1975) (administered to Cambridge patients only); KOLT = Kendrick Object Learning Test (Kendrick, 1985) (administered to London patients only); onset = age at onset (in years) of chorea; Duration = duration (in years) of chorea; HD = patients with early Huntington's disease. CS = control subjects; CS2 = separate control subjects for visual discrimination learning/attentional set shifting task; n/a = not appropriate.

of this task, subjects were given the following cognitive tasks in the order described below.

**Pattern and spatial recognition**

Two tasks designed to assess recognition memory for both patterns and spatial locations were administered (Sahakian et al., 1988). In the pattern recognition task, subjects are presented with a series of 12 abstract patterns and their task is to remember them. Following a 5-s delay, each pattern is re-presented in reverse order, paired with a novel pattern and subjects are asked to touch the pattern they have seen previously. This procedure is then repeated with a further 12 patterns.

In the spatial recognition task, five squares are presented sequentially in different locations around the screen. In the recognition phase, subjects are presented with a choice of two squares in different locations, one of which is novel; they must touch the location in which the square has previously appeared. This procedure is repeated a further three times.

**Spatial span**

This is a computerized version of the Corsi block-tapping task (Milner, 1971). Each trial begins with nine white boxes presented in fixed locations on the monitor screen (Owen et al., 1990). Initially, two of the boxes change colour, one after the other, in a pre-determined sequence. The end of the sequence is indicated by a tone. Subjects are then asked to point to the boxes in the order in which they have changed colour. After successful completion of a sequence, the number of boxes changing colour increases by one, up to a maximum of nine. The test is terminated when three consecutive failures occur at any one sequence length.
Spatial working memory
This is a test of spatial working memory for humans (Owen et al., 1990), which is formally analogous to the Olton radial arm maze (Olton and Samuelson, 1976), a task of spatial working memory for the rat. Both tasks require memory for locations already visited. In this task, subjects are required to 'search through' a number of coloured boxes presented on the monitor screen (by touching each one), in order to find blue 'tokens' which are hidden inside. On any one trial, only a single token is hidden in one of the boxes. Once found, the next token is hidden. The key instruction is that once a token has been found within a particular box, then that box will not be used again to hide a token. Two error-types are possible. First, a subject may return to open a box in which a token has already been found (a 'between-search' error). Secondly, a subject may return to a box already opened and shown to be empty earlier in the same trial (a 'within-search' error). There are four trials with each of four, six and eight boxes. The task is scored according to the number of between- and within-search errors at each level of difficulty and also for the use of an efficient search strategy (Owen et al., 1990). A particularly efficient strategy for completing this task is to follow a predetermined search sequence, starting with a particular box and then returning to start each new sequence with that same box as soon as a token is found (editing the sequence when a token is found in that box). The extent to which such a strategy is used is estimated from the number of search sequences starting with a novel box for just the more difficult six- and eight-box problems. The total of these scores provides a measure of strategy for each subject, with a high score (many sequences starting with a novel box) representing poor use of a strategy and vice versa.

Tower of London
The Cambridge Neuropsychological Test Automated Battery contains a modified version of the Tower of London spatial planning task (Shallice, 1982), in which it is possible to measure the speed and accuracy of thinking. In the problem-solving condition, subjects have to move coloured balls between suspended vertical 'stockings' represented on the monitor screen in order to establish a goal position in a specified number of moves (Owen et al., 1990). In a yoked control condition, the computer 'plays back' the solution to each problem using the sequence of moves actually employed by the subject, a single move at a time. The subject has to copy each individual move without having to plan them, as part of a sequence. Subtraction of the latencies to move the balls in the yoked control condition from that in the problem-solving condition provides a measure of thinking time. The accuracy of thinking can be measured in a number of ways, the most stringent being the proportion of problems solved in the minimum specified number of moves (the number of 'perfect' solutions). A less stringent measure is the number of moves taken in excess of the specified minimum number, but within the maximum allowed.

Visual discrimination learning/attentional set shifting
This task of discrimination learning has been described in greater detail elsewhere (Roberts et al., 1988; Downes et al., 1989). The task requires subjects to learn a series of two-alternative forced-choice discriminations using feedback provided automatically by the computer. The task is composed of nine stages presented in the same fixed order, starting with a simple discrimination and its reversal for stimuli varying in just one dimension (e.g. two different white line configurations). A second, alternative dimension is then introduced (purple filled shapes) and compound discrimination and reversal are tested. To succeed, subjects must continue to respond to the previously relevant dimension whilst ignoring the presence of the new, irrelevant dimension. At the intradimensional shift stage, novel exemplars of each of the two dimensions are introduced and subjects must continue to respond to one of the two exemplars from the previously relevant dimension. Following another reversal, the EDS and its reversal are presented, again using novel exemplars of each stimulus dimension. In order to succeed at this stage, the subject must shift 'response set' to the previously irrelevant stimulus dimension, whilst ignoring the previously relevant dimension. The EDS stage is akin to a change in category in the Wisconsin Card Sorting Test.

Data analysis
The majority of the experimental data were analysed using the statistical packages STATWORKS (Cricket Software Inc., Philadelphia, Penn., USA), CLR ANOVA (Clear Lake Research Inc., USA) and SPSS V4.0 (SPSS Inc., Chicago, Ill., USA) running on an Apple Macintosh SE/30 computer. Data were transformed where appropriate (Tukey, 1977). Test variables were compared using ANOVA. The ANOVA model was a two-factor design with group and difficulty level as factors. Student's t tests were applied to test the significance of differences between means where factorial ANOVA was not required. Where appropriate, Pearson product moment and Spearman rank order correlation coefficients were calculated.

For the attentional set shifting task, the data for the number of subjects passing or failing at each stage of the task were cast into contingency tables and analysed using the likelihood ratio method (Kullback, 1968; Robbins, 1977), which is useful for analysing data with small cell frequencies and for partitioning inhomogeneities in the contingency table by additive, orthogonal contrasts. The resulting 'information statistic' (2i) is distributed as $\chi^2$.

Results
Pattern and spatial recognition memory
The mean percentage correct scores for both the pattern and spatial recognition memory tests are presented in Table 2.
Unpaired \( t \) tests revealed that the Huntington's disease patients performed significantly worse than control subjects on both pattern \( t(34) = 4.05, P < 0.001 \) and spatial \( t(34) = 3.69, P < 0.002 \) recognition. A paired \( t \) test revealed that control subjects found spatial recognition more difficult than pattern recognition \( t(17) = 2.36, P < 0.03 \), whereas this was not the case for the Huntington's disease patients \( t(17) = 0.74, P > 0.4 \).

The mean response latencies for both tasks were also compared, following logarithmic transformation to reduce positive skew in the distribution. Unpaired \( t \) tests revealed that the Huntington's disease group were significantly slower than controls on the pattern recognition task \( t(34) = 4.29, P < 0.001 \) and also the spatial recognition task \( t(34) = 2.02, P = 0.05 \).

**Spatial span**

Mean spatial spans for the two groups are presented in Table 2. Huntington's disease patients had a significantly shorter spatial span than did their control subjects \( t(34) = 4.20, P < 0.001 \).

**Spatial working memory**

The mean number of 'between-search' errors made at each stage of the task by the two groups can be seen in Fig. 1. Scores were compared using two-way ANOVA, with group and level of difficulty as factors. There was a significant main effect of group \( F(1,34) = 14.33, P = 0.0006 \) and a significant main effect of difficulty \( F(2,68) = 84.72, P < 0.0001 \). There was also a significant interaction between the group and difficulty factors \( F(2,68) = 8.09, P = 0.0007 \). Further analysis of simple main effects revealed that the Huntington's disease group made significantly more 'between-search' errors than control subjects at all levels of task difficulty [four boxes, \( F(1,34) = 7.63, P = 0.009 \); six boxes, \( F(1,34) = 11.17, P = 0.002 \); eight boxes, \( F(1,34) = 12.16, P = 0.001 \)]. Within-search errors were at a minimal level in both groups and hence no meaningful analysis was possible.

In addition, an unpaired \( t \) test revealed that the Huntington's disease group made significantly less use of an efficient search strategy \( t(34) = 2.39, P = 0.02 \). The mean strategy score for Huntington's disease patients was 34.1 (SD 6.6) compared with 29.6 (SD 4.5) for controls. The relationship between strategy score and number of errors obtained on the spatial working memory task was further examined using Pearson's product moment correlation coefficient, \( r \). As expected, there was a significant correlation between strategy score and number of 'between-search' errors for both controls \( r(18) = 0.65, P < 0.01 \) and patients \( r(18) = 0.76, P < 0.01 \). These correlation coefficients did not differ significantly from one another. Analysis of covariance, covarying for strategy scores, still resulted in a group difference in between search errors at the higher levels of difficulty \( F(1,33) = 4.44, P = 0.04 \). This suggests that although an impairment in the implementation of an efficient search strategy is the major contributing factor to Huntington's disease patients' poor spatial working memory performance, it is not the only such factor.

**Tower of London**

**Accuracy measures**

Across the 12 test problems, two measures relating to accuracy of planning were calculated. The proportion of 'perfect' solutions provided the most stringent measure of planning. The mean number of excess moves provided a more general measure of group performance at each level of difficulty. The results for the two groups are presented graphically in Fig. 2A and B. ANOVA revealed that for the proportion of 'perfect' solutions there was a significant main effect of difficulty for both groups \( F(3,102) = 21.69, P < 0.0001 \) and a significant main effect of group \( F(1,34) = 6.39, P = 0.016 \) but no interaction between group and difficulty factors, although this did approach significance \( F(3,102) = 2.31, P = 0.08 \).
Fig. 2 A–D Proportion of 'perfect' solutions; mean number of excess moves; mean initial thinking times per move; mean subsequent thinking times per move, all as a function of problem difficulty (i.e. moves required) on the Tower of London. Error bars represent 1 SEM. Filled circles = patients with early Huntington's disease; open circles = control subjects.

For the mean number of excess moves there was a significant main effect of difficulty \([F(3,102) = 29.56, P < 0.0001]\), but no main effect of group \([F(1,34) = 3.58, P > 0.05]\). There was, however, a significant group \(\times\) difficulty interaction \([F(3,102) = 4.03, P < 0.01]\). Further analysis of simple main effects revealed that this was a result of the Huntington's disease patients making significantly more excess moves on five-move problems only.

**Movement times**

Baseline measures of motor initiation time and motor execution time were extracted from the 12 yoked control trials. The motor initiation time represented the mean time between the onset of each problem and the completion of the first selection, i.e. a correct touch of the required ball.

For patients and controls, average initial movement times varied between 3.1 and 5.1 s and 1.9 and 2.6 s, respectively and mean motor execution times varied between 2.4 and 4.2 s and 1.4 and 1.7 s, respectively. ANOVA revealed that there was a significant main effect of group \([F(1,34) = 9.46, P = 0.004]\). Thus the Huntington's disease group were slower in terms of their initial movement times. Further, the Huntington's disease group were slower in terms of their motor execution time, i.e. the time between selection of the first ball and completion of the problem \([F(1,34) = 22.17, P < 0.0001]\). Also, motor initiation \([F(3,102) = 4.76, P = 0.004]\) and execution \([F(3,102) = 6.88, P = 0.003]\) times decreased as problem difficulty increased, most probably reflecting practice effects. Group \(\times\) difficulty interactions were not significant.

**Thinking times**

The initial thinking time was the interval between presentation of the problem and the first touch of a ball, minus the corresponding motor initiation time. The subsequent thinking time was the time between the first touch of a ball and the completion of the entire problem minus the total motor execution time derived from the corresponding control problem. As subsequent thinking time varied with the length of the problem, this measure was divided by the number of moves made when solving that same problem to give an estimate of thinking time per move. Initial and subsequent thinking times per move for the two groups are shown in Fig. 2C and D.
Cognition in early Huntington's disease

1.0 - 0.9 - 0.8 - 0.7 - 0.6 - 0.5 - 0.4 - 0.3 - 0.2 - 0.1 - 0.0

**Fig. 3** Cumulative failure rate at each stage of the visual discrimination learning/attentional set shifting task. Filled circles = patients with early Huntington's disease; open circles = control subjects.

The Huntington's disease patients were significantly slower in terms of both their initial thinking times \( F(1,34) = 13.19, P = 0.0009 \) and subsequent thinking times (for problems solved within the maximum allowed) \( F(1,34) = 9.21, P = 0.005 \). Further, both initial \( F(3,102) = 52.39, P < 0.0001 \) and subsequent \( F(3,102) = 13.60, P < 0.0001 \) thinking times increased with increasing problem difficulty. Group \( \times \) difficulty interactions were not significant.

**Visual discrimination learning/attentional set shifting**

Figure 3 shows the cumulative proportion of subjects succeeding at each stage of the task. As can be seen, fewer than 20% of Huntington's disease patients, compared with more than 75% of control subjects, successfully completed all stages of the task. Likelihood ratio analysis of the contingency tables for success and failure confirmed that this difference was significant \( 2\chi(1) = 24.66, P < 0.001 \). Additional analyses were undertaken in order to identify the stages at which the differences in cumulative failure became significant. In cumulative terms, there was not a significant difference between controls and Huntington's disease patients by the intradimensional reversal stage \( 2\chi(1) = 2.40, P > 0.1 \), suggesting that Huntington's disease patients did not have difficulty forming and maintaining response sets. A final comparison was made at the EDS stage, including only those subjects able to attempt that stage. The Huntington's disease group were significantly impaired relative to control subjects \( 2\chi(1) = 27.08, P < 0.001 \). Thus patients with early Huntington's disease were impaired in the shifting, but not the formation or maintenance of response set.

Response latencies were also analysed using an ANOVA design, following logarithmic transformation to reduce positive skew in the distributions. There was a significant effect of stage \( F(7,280) = 57.9, P < 0.001 \) but no effect of group \( F(1,40) = 0.7, P = 0.41 \) and no group by stage interaction \( F(7,280) = 0.7, P = 0.68 \). Response latencies are plotted in Fig. 4.

**Correlational analyses**

Pearson product moment correlations were calculated between age; age of onset and duration of chorea and all relevant cognitive variables. There were significant correlations between age and subsequent movement times on the Tower of London \( r = 0.57, P < 0.05 \); age at onset and motor screening latencies \( r = 0.49, P < 0.05 \) and age at onset and subsequent movement times on the Tower \( r = 0.58, P < 0.05 \); correlations with several other of the cognitive variables (spatial span, spatial recognition and Tower thinking times) also approached significance \( P < 0.1 \). In contrast, disease duration did not correlate with any variable. These results are important in the light of the suggestion that duration of illness is a poor indicator of degree of neuropathology in Huntington's disease, whereas age at onset is a greater indicator of neuropathological severity, suggesting that patients with different ages of onset could have very different neuronal degeneration at equivalent disease durations (Myers et al., 1988).

Additional correlations were made between motor screening latencies and scores on the cognitive tasks for Huntington's disease patients, to assess the possible contribution of motor difficulties to cognitive impairment.
Only spatial span correlated significantly with motor screening latencies \( r = -0.54, P < 0.05 \), suggesting that only spatial span was affected by motor difficulties.

**Discussion**

In this study we examined the cognitive performance of patients in the early stages of Huntington's disease on a range of tests of executive and visuospatial mnemonic function. These tests have already been shown to reveal deficits in late Huntington's disease which are significantly greater than those observed in patients with Alzheimer's disease, matched for degree of dementia (Lange et al., 1995). The results show that even early in the course of the disease when they are largely unimpaired in activities of daily living, Huntington's disease patients show a wide range of cognitive impairments encompassing both executive and visuospatial mnemonic functions, although the magnitude of the deficits is smaller than in late Huntington's disease. These deficits, however, cannot be attributed to global intellectual or motor difficulties. For instance, the planning deficits on the Tower of London are only apparent at the highest levels of difficulty; there is a sparing of set formation and maintenance; and the impairment in pattern recognition is much greater than that in spatial recognition, as evidenced by response latencies, suggesting particular difficulties in visual object recognition memory. In addition, only spatial span correlated significantly with motor screening latencies in Huntington's disease patients.

By comparing the performance of the early and late Huntington's disease groups on the same tasks we are able to obtain a profile of the progression of cognitive deficits in Huntington's disease, similar to that already reported for Parkinson's disease (Owen et al., 1992). The use of a common battery, including tests differentially sensitive to frontal and temporal lobe dysfunction, also allows a direct comparison between these two forms of basal ganglia disorder that can be related to the pattern of neuropathology in the striatum and its cortico-striatal circuitry. The comparison with Parkinson's disease shows that while the pattern of deficits in early Huntington's disease is somewhat similar to that of patients with clinically severe Parkinson's disease, important differences are present, notably in pattern recognition memory.

**Staging of set-shifting deficits in Huntington's disease**

The most striking deficit seen in the Huntington's disease group was in their performance on the visual discrimination learning/attentional set shifting task. They were impaired specifically at the EDS stage, with fewer than 20% of the Huntington's disease patients able to reach the criterion of six consecutive correct responses within 50 trials. This is a far greater impairment than that seen in patients with frontal lobe lesions of a similar age (Owen et al., 1991) and is comparable to that found in patients with clinically severe progressive supranuclear palsy (Robbins et al., 1994). The deficit is also greater than that seen in unmedicated, early-in-the course patients with Parkinson's disease where, however, there is typically greater attrition in the earlier, set-forming stages of the task (Owen et al., 1992). Furthermore, patients with mild dementia of Alzheimer type with similar scores on the Mini-Mental State Examination are unimpaired on the EDS stage of this task, but show marked visuospatial memory deficits, thus ruling out an explanation in terms of a global cognitive impairment (Sahakian et al., 1990). Moreover, the deficit was specific to the EDS stage of the task: Huntington's disease patients were not impaired on the earlier stages of the task, showing that this shifting impairment is confined to the level of shifting between perceptual dimensions and that patients with early Huntington's disease do not have difficulty in the formation and maintenance of response set. These findings are in agreement with Josiassen et al. (1983) who found an increase in perseverative, but not non-perseverative errors on the Wisconsin Card Sorting Test in early Huntington's disease.

The increases in perseverative responding at the EDS stage in the early Huntington's disease patients are not observed in the reversal learning phases of this paradigm. However, in late Huntington's disease, we have shown that patients exhibit dramatic increases in perseveration in the reversal phases of the task, preventing them from reaching the EDS stage. These deficits are truly perseverative because the patients continue to select the formerly reinforced stimulus to a significant degree. The results from the two studies suggest that perseverative behaviour, presumably arising from an inability to switch between response sets, is a cardinal feature of Huntington's disease, but that its expression varies according to the course of the disease. It can be argued that reversal learning and extra-dimensional shifting represent two distinct levels of an hierarchy of inhibitory associative and attentional mechanisms by which responding is normally controlled (Sutherland and Mackintosh, 1971). It appears that in Huntington's disease this hierarchy of inhibitory processes collapses, presumably at least partly via neuropathological changes at the level of the striatum, especially the head of the caudate nucleus. The data from Huntington's disease patients thus agree with the hypothesis that a major function of the striatum is to mediate aspects of 'response set' (Alexander et al., 1986; Chevalier and Deniau, 1990; Robbins and Brown, 1990), including cognitive as well as motor functions.

**Anatomical and neuropathological implications of set shifting deficit**

The results with the attentional set-shifting task are of additional interest as almost exactly the same task has been used with non-human primates. Recent findings show doubly
dissociable effects of lesions to different portions of the prefrontal cortex on the extra-dimensional shifting and reversal phases of the visual discrimination learning/attentional set shifting paradigm in non-human primates. Marmosets with lesions of Brodmann area 9 exhibit deficits in the extra-dimensional shift, whereas lesions of the orbitofrontal cortex selectively impair reversal learning (Dias et al., 1996). Anatomical evidence in monkeys suggests that these regions of the prefrontal cortex project to dorsal aspects of the caudate nucleus in the case of the dorsolateral prefrontal cortex and to ventromedial regions in the case of orbitofrontal prefrontal cortex (Alexander et al., 1986; Yeterian and Pandya, 1994), thus possibly constituting distinct cortico-striatal ‘loops’.

These anatomical results, which suggest that the reversal deficits might be related to the ventromedial head of the caudate nucleus, whereas the shifting deficits may be related to more dorsal regions of the head of the caudate, thus fit with what is known about the neuropsychological progression of Huntington’s disease in which neuronal loss begins with the striosome compartment of the head of the caudate and progresses in a dorsal-to-ventral direction (Hedreen and Folstein, 1995). Striosomes in the dorsal regions of the caudate receive input primarily from dorsal prefrontal cortex, whereas those in more ventral regions of the caudate receive input from limbic-related areas (Gerfen, 1992). Therefore, the dorsal-to-ventral striatal pathology in Huntington’s disease effectively leads to disruption of the output of the computations of the prefrontal cortex in a dorsal-to-ventral direction, with those functions associated with dorsolateral prefrontal cortex being disrupted before those associated with orbitofrontal regions.

### Planning impairments in Huntington’s disease and their cognitive components

The ability to plan or ‘look ahead’ is another central component of executive function (Tranel et al., 1994). In previous studies of planning in Huntington’s disease, various versions of the Tower of Hanoi task have been used (Butters et al., 1985; Saint-Cyr et al., 1988). Using a five-disc version of the Tower of Hanoi, Butters et al. (1985) failed to find significant deficits in a group of early Huntington’s disease patients. Saint-Cyr et al. (1988) did find impairments in a small subset of four Huntington’s disease patients on the four-disc ‘tower of Toronto’. However, the methods used in both of these studies may not have provided a true indication of the ability to plan. Goel and Grafman (1995) have argued that completion of these tasks does not necessitate the formulation and implementation of a plan because the solutions can be ‘edited’ on-line and the repetitive trial and error learning is more akin to procedural learning than to ‘look ahead’ planning. They agree that the present, single trial, Tower of London task provides a purer measure of this ‘look ahead’ function in planning. The importance of this point is shown by the fact that across all problems, the Huntington’s disease patients in this study were only impaired on the most stringent index of planning efficiency, the number of ‘perfect’ solutions, and only made more excess moves than control subjects on the most difficult five-move problems.

Patients with early Huntington’s disease were also impaired in terms of their initial and subsequent thinking times, after correction for motor slowing. These results are thus also consistent with findings of severe bradyphrenia in Huntington’s disease (Sprengelmeyer et al., 1995). This pattern of results is qualitatively different from that seen in either frontal lobe excision patients (Owen et al., 1990) or in patients with other forms of basal ganglia disorder such as Parkinson’s disease, progressive supranuclear palsy or multiple system atrophy (see Table 3). The Huntington’s disease patients in this study can be seen to show deficits in thinking time consistent with both striatal and frontal lobe dysfunction. It is unlikely that these qualitative differences with the other disorders simply reflect the overall severity of the impairment, because the impairment in producing ‘perfect’ solutions is of a similar level to that of frontal lobe excision patients (Owen et al., 1990). These specific deficits in performance on the Tower of London in early Huntington’s disease are also present in late Huntington’s disease to a greater extent than in patients with dementia of Alzheimer type matched for level of dementia (Lange et al., 1995). However, there is evidence for considerable progression in the nature of the impairment in late Huntington’s disease, with markedly impaired accuracy even at two and three move problems. Such deficits probably reflect a breakdown in the elementary perceptual functions that contribute to higher order planning functions.

As the planning deficit on the Tower of London task may
Anatomical and neuropathological implications of planning and memory deficits in Huntington’s disease

The deficits in spatial memory in early Huntington’s disease are perhaps not surprising in the light of primate studies (e.g., Friedman and Goldman-Rakic, 1994), which have revealed that spatial working memory is subserved by a distributed network encompassing the dorsolateral prefrontal cortex and posterior parietal cortex. The dorsolateral prefrontal cortex is implicated in working memory processes (Petrides, 1994), whilst the parietal cortex is known to play a crucial role in visuospatial processing (Ungerleider and Haxby, 1994). Moreover, a recent PET study (Owen et al., 1996) has shown a role for these regions in the performance of spatial span and spatial working memory tasks analogous to the ones used in this study. There are heavy projections from posterior parietal cortex to the dorsal regions of the caudate nucleus (Baizer et al., 1993; Vonsattel and Pandya, 1993). The dorsal caudate nucleus may thus form part of the ‘where’ or parietal stream involved in visuospatial functions (Ungerleider and Haxby, 1994). The dorsolateral prefrontal cortex and posterior parietal areas have common projections to the dorsal caudate nucleus (Seelen and Goldman-Rakic, 1988) and hence it is not surprising that damage to the dorsal portions of the caudate nucleus in early Huntington’s disease results in impaired spatial working memory, again consistent with the disruption of distinct cortico-striatal ‘loops’.

The impairments in visual pattern recognition memory seen in the current Huntington’s disease patients are consistent with the results of other studies (Moss et al., 1986; Lundervold et al., 1994), but contrast with our findings that patients with Parkinson’s disease generally show no deficits on this task at even severe levels of clinical disability, although impairments are apparent in Parkinson’s disease patients who are close to meeting the clinical criteria of dementia (Owen et al., 1993). The present pattern recognition memory impairment has also been observed in patients with temporal lobe lesions or amygdalo-hippocampectomy (Owen et al., 1995). Such deficits are associated with damage to a circuit connecting inferotemporal cortex with the perirhinal and entorhinal cortices (Mishkin and Murray, 1994).

Connections from inferotemporal cortex project heavily to the ventrocaudal neostriatum (ventral putamen and tail of the caudate) (Yeterian and Pandya, 1995). Thus, the ventrocaudal striatum may form part of an inferotemporal (or ‘what’) stream, processing visual objects (Ungerleider and Haxby, 1994). Whilst there have been relatively few functional studies of these visual pathways, lesion (Divac et al., 1967; Buerger et al., 1974) and electrophysiological (Rolls, 1994; Brown et al., 1995) studies confirm they have important functions in visual processing, which bear on the present deficit seen in Huntington’s disease, as some of the earliest pathological changes in Huntington’s disease have been reported to occur in the tail of the caudate nucleus (Vonsattel et al., 1985). Although some authors have found temporal lobe damage in post-mortem Huntington’s disease brains (de la Monte et al., 1988; Mann et al., 1993), PET imaging studies of early Huntington’s disease patients show normal temporal lobe metabolism (Martin et al., 1992). Hence, it seems likely that the impaired pattern recognition memory of early Huntington’s disease patients is a result of damage to the ventrocaudal striatum. A similar conclusion has recently been reached by Jacobs et al. (1995), who found impaired facial recognition in early Huntington’s disease. However, in the absence of neuroimaging data for the patients, we cannot definitively exclude the possibility of cortical atrophy that might produce a similar deficit.

In conclusion, the range of cognitive deficits seen in early Huntington’s disease is consistent with a distinct striatal
pathology which leads to deficits in tests of executive function probably dependent upon intact fronto-striatal function, but also to impairment of basic cognitive functions, some of which are qualitatively distinct from those in the early stages of other basal ganglia disorders. By means of a cross-sectional comparison with patients with advanced Huntington's disease (Lange et al., 1995) we have shown that major features of the cognitive decline seen in Huntington's disease are abilities in switching response set and failures in monitoring responses in self-ordered memory tasks. These deficits may lead to cognitive impairments at different stages of the disease that may appear qualitatively distinct (e.g. set shifting versus simple reversal). However, such impairments may reflect a gradual deterioration of mechanisms of response inhibition operating at different levels of processing, but under the control of fronto-striatal circuitry.

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