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The relationship between striatal dopamine receptor binding and cognitive performance in Huntington's disease

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Summary

Seventeen individuals at risk for Huntington's disease and five symptomatic patients, who had previously undergone [^{11}C]SCH23390 and [^{11}C]raclopride PET to assess in vivo levels of striatal dopamine D_1 and D_2 receptor binding, had neuropsychological assessment on a series of tests known to be sensitive to symptomatic Huntington's disease, including tests of verbal fluency, memory, attention and planning. Compared with age- and IQ-matched healthy volunteers, clinically symptomatic carriers of the Huntington's disease mutation were found to be impaired on tests of verbal fluency, spatial span, planning and sequence generation, as were clinically asymptomatic Huntington's disease mutation carriers. In asymptomatic individuals, both striatal dopamine receptor levels and cognitive performance were lower in subjects approaching their estimated age of onset. In addition, performance on these tasks was found to correlate with PET measures of striatal D_1 and D_2 receptor binding levels, especially D_2 binding. These results are consistent with a role for the striatum, as part of the complex corticobasal ganglia–thalamocortical circuitry, in the optimal scheduling and sequencing of responses, and suggest that cognitive manifestations of striatal dysfunction can be evidenced in carriers of the Huntington's disease mutation prior to the onset of overt clinical movement disorder.

Keywords: Huntington's disease; PET; dopamine; sequencing; working memory

Abbreviations: ADL = activities of daily living; AR^+ = at risk—subjects with Huntington's disease mutation; AR^- = not at risk—subjects negative for Huntington's disease mutation; $AR^?$ = subjects who may be at risk for Huntington's disease but who declined the test; CS = control subjects; CANTAB = Cambridge Neuropsychological Test Automated Battery; EDS = extradimensional shift; EDR = reversal of extradimensional shift; IQR = interquartile range

Introduction

In previous work (Lawrence *et al*., 1996; Lawrence, 1997) we have established that patients with clinically symptomatic Huntington's disease exhibit a progressive cognitive decline that can be related to the progression of neuronal degeneration throughout the striatum (Vonsattel *et al*., 1985; Hedreen and Folstein, 1995). An area of much controversy relates to whether or not the cognitive deficits seen in Huntington's disease are the result of damage to the striatum itself, or of the cortical degeneration that is known to be present in Huntington's disease (see e.g. De la Monte *et al*., 1988; Mann *et al*., 1993; Heinsen *et al*., 1994).

A number of neuroimaging studies have reported significant correlations between structural and functional indices of striatal integrity and measures of cognitive function, especially executive function, memory and psychomotor speed (Berent *et al*., 1988; Hasselbalch *et al*., 1992; Starkstein *et al*., 1992; Bamford *et al*., 1995) in symptomatic Huntington's disease. In addition, Goldberg *et al*. (1990), using a xenon-inhalation functional activation paradigm, have shown that performance on the Wisconsin Card Sorting Test in Huntington's disease is associated with increased blood flow, relative to healthy volunteers, in the prefrontal cortex,

and that a functionally intact frontal cortex is having to 'work harder' in order to overcome striatal dysfunction. However, other studies have reported that cortical dysfunction, especially of the frontal and temporal cortices, is a better correlate of cognitive impairment than is striatal atrophy (e.g. Harris *et al*., 1996; Sax *et al*., 1996). It is thus unclear from these studies to what extent cognitive dysfunction in Huntington's disease is a result of striatal as opposed to cortical dysfunction.

Of particular interest in this regard are data from preclinical carriers of the Huntington's disease mutation. An examination of the available neuropathological and neuroimaging data suggests that basal ganglia dysfunction can be evidenced in subjects prior to the onset of clinical symptomatology. Albin *et al.* (1990, 1992) have shown *post mortem*, in a single subject with preclinical Huntington's disease, a preferential loss of striatal neurons projecting to the external segment of the globus pallidus. Recent *in vivo* neuroimaging studies have shown reduced striatal volumes on MRI (Aylward *et al*., 1994, 1996), decreased striatal D_2 receptor binding on SPECT (single proton emission computed tomography) and PET imaging (Ichise *et al*., 1993; Antonini *et al*., 1996; Weeks *et al*., 1996) and reduced striatal glucose consumption on PET imaging (Mazziotta, 1990; Grafton *et al*., 1992; Kuwert *et al*., 1993; Antonini *et al*., 1996) in subpopulations of subjects with preclinical Huntington's disease.

In a recent paper (Weeks *et al*., 1996) we have shown, using PET, a significant, parallel reduction in dopamine D_1 and D_2 receptor binding in the caudate and putamen of four out of eight asymptomatic carriers of the Huntington's disease mutation and one out of six subjects with a 50% risk of having Huntington's disease. Abnormalities were more common in gene carriers nearer the typical Huntington's disease age of onset relative to younger subjects. These results were somewhat surprising, given current models of choreic Huntington's disease (Albin, 1995; Hedreen and Folstein, 1995), which posit that the D_2-bearing 'indirect' pathway via the globus pallidus and subthalamic nucleus to the internal globus pallidus is targeted preferentially compared with the 'direct' striatal output pathway to the internal globus pallidus, which is rich in D_1 receptors. However, recent studies by Beal and colleagues (for review, see Ferrante *et al*., 1994) have found no evidence for preferential neuronal loss in the indirect pathway in any neuropathological grade of Huntington's disease, in line with the results of Weeks *et al*. (1996). PET studies in clinically affected Huntington's disease patients have also shown parallel reductions of striatal D_1 and D_2 binding (Turjanski *et al*., 1995; Ginovart *et al*., 1997).

The purpose of the present study was to examine performance of both symptomatic and presymptomatic subjects on cognitive tests which we have found to be sensitive to Huntington's disease, in order to determine how the cognitive impairment seen in Huntington's disease relates to the degree of loss of dopamine receptor binding in the striatum, as measured by PET. Although there have been a number of studies examining the relationships between striatal integrity and cognitive performance in clinically symptomatic Huntington's disease, no studies to date have examined the relationship between cognitive performance and striatal dopamine binding in subjects at risk for Huntington's disease. This group of subjects is particularly appropriate for examining the proposed cognitive functions of the striatum, as it is unlikely at this stage that extrastriatal pathology is present (Albin *et al*., 1992).

Method

Subjects

Seventeen subjects at risk of developing Huntington's disease and five clinically symptomatic Huntington's disease patients were studied. All at-risk subjects were asymptomatic and had normal neurological examinations. All subjects had PET scans prior to neuropsychological testing. One subject was taking antidepressant medication. None of the subjects were taking medication known to cause postsynaptic dopaminergic blockade, or known to impair cognition. Cognitive assessment was carried out by two of us (A.D.L. and L.H.A.W.) blind to both gene status and PET scan results. One at-risk subject suffered from claustrophobia and declined to be scanned. Her neuropsychological data were included in the analysis reported below.

The study was approved by the ethics committee of the Royal Postgraduate Medical School, Hammersmith Hospital, London. Permission to administer [^{11}C]raclopride and [^{11}C]SCH23390 was obtained from the Administration of Radioactive Substances Advisory Committee of the UK. All subjects gave written informed consent.

Predictive and diagnostic testing

DNA analysis for the Huntington's disease mutation was performed as described by Davis *et al*. (1994) in 13 subjects. Eight had the Huntington's disease mutation and five did not. Four relatives of Huntington's disease patients decided against testing or deferred the test and thus remain at 50% risk. We designate the Huntington's disease mutation carriers as group AR^+, non-carriers as AR^- and at-risk as $AR^?$ Five subjects who were considered by an experienced neurologist (R.A.W. or T.C.A.) to have met clinical criteria for Huntington's disease had the diagnosis confirmed by means of a diagnostic gene test.

Material and procedures

Scan procedure

At-risk subjects had [^{11}C]SCH23390 and [^{11}C]raclopride PET to assess D_1 and D_2 dopamine receptor binding respectively. The scans were performed on consecutive days, with a CTI 931/-08/12 (raclopride) or 953B (SCH23390) camera at the MRC Cyclotron Unit, Hammersmith Hospital. Full details of

the scan procedure and data analysis can be found in Weeks *et al*. (1996). CT or MRI scans were not available for any subject.

Neuropsychological tests

Standard psychometric assessment

Each subject was administered the National Adult Reading Test (Nelson, 1982), which is a reading-based estimate of premorbid IQ; a letter fluency test (Benton and Hamsher, 1976), in which subjects are asked to generate as many words as possible beginning with the letters F, A and S, in that order, allowing 1 min/letter; and a semantic fluency test (Goodglass and Kaplan, 1983), in which subjects must generate the names of as many animals as possible in 90 s.

Computerized cognitive tests

The following tests were administered using a portable CARRYI 486 microcomputer (CARRYI, Taiwan) fitted with a Datalux touch-sensitive screen. The motor screening, pattern and spatial recognition memory, spatial span and spatial working memory tasks form part of the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Pattern and spatial recognition memory. 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 each location is re-presented and paired with a novel location, and subjects are asked to touch the location in which they have seen a square appear. This procedure is repeated a further three times.

Spatial span. This is a computerized version of the Corsi block-tapping task (Milner, 1971). Briefly, each trial begins with nine white boxes presented in fixed locations on the monitor screen (for details, see Owen *et al*., 1990). Initially, two of the boxes change colour, one after the other, in a predetermined 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 1, up to a maximum of 9. The test is terminated when three consecutive failures occur at any one sequence length.

Spatial working memory. 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 types of error 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, a high score (many sequences starting with a novel box) representing poor use of a strategy and vice versa.

Sequence generation. Subjects are instructed to generate as many novel four-box sequences as possible, in 24 trials, by touching each of four squares, organized in compass fashion, in turn (Owen *et al*., 1995). The maximum number of novel sequences that can be generated is 24. As each square is touched, it changes colour for 10 ms and a high-pitched tone is sounded over the same duration. After a four-box sequence has been completed, a middle-pitched tone is sounded if the sequence is novel, or a low-pitched tone if the sequence is a repetition of a previous one. There are no time limits, and responses are not paced. Feedback is provided by means of a score counter presented in the centre of the screen.

After an initial phase of 24 trials, two further phases are administered. The first of these is a training phase, in which subjects are demonstrated an effective strategy for task-performance. One of the four boxes is highlighted and the subject is told to find the six four-box sequences beginning with that box. This procedure is then repeated for the remaining three boxes. The final phase (phase 2), designed to assess the efficacy of this training procedure, is a replication of phase 1.

One-touch Tower of London task. This task is a modified version of the CANTAB Tower of London task (for full details, see Owen *et al*., 1995). Subjects are first trained with a number of problems from the original Tower of London task and then presented with the following modified

task. Two sets of coloured balls appear on the screen, one in the upper half of the screen and one in the lower half. They are described to the subjects as 'snooker' balls as they appear to hang in vertical pockets. There are three pockets in each half of the screen, one capable of holding three balls, one able to hold two balls and one able to hold one ball. The numbers 1, 2, 3, 4 and 5 are printed in large boxes across the bottom of the screen. At the start of each trial the upper and lower pockets appear empty on the screen. After a 1-s delay, a tone alerts the subject to the screen and a red ball, a blue ball and a green ball are placed in a predetermined arrangement in the pockets of the upper and lower displays. The subjects are instructed to examine the positions of the balls on the screen and then to imagine how they might rearrange the balls in the lower display to match those in the upper display without actually moving any of the balls. For any given arrangement, the subject is asked to find the solution that requires the minimum number of moves, and then to press the corresponding number on the bottom of the screen. If the first response is incorrect the subject is required to try again until the correct number is selected. The importance of accuracy rather than speed of response is emphasized. There are 20 trials of varying problem difficulty arranged in a constant, pseudorandom order.

Visual discrimination learning/attentional set-shifting. This test is a modified version of the CANTAB attentional set-shifting task (Owen *et al*., 1993). Subjects are required to perform a series of two-alternative, forced-choice discriminations using feedback provided automatically by the computer, in two conditions, labelled 'perseveration' and 'learned irrelevance'. At each stage of the task the criterion is six consecutive correct responses, and the next stage begins automatically once that criterion has been achieved. Each condition comprises eight stages presented in the same fixed order, starting with a simple discrimination and its reversal for stimuli varying in just one dimension. A second, alternative dimension is then introduced 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 extradimensional shift (EDS) and its reversal (EDR) are presented. At the EDS stage, the two conditions diverge. In the 'perseveration' condition the previously irrelevant dimension is replaced by a novel dimension. Subjects must respond to the novel dimension. Failure to make an attentional shift cannot therefore be due to prior learning about the new dimension, and must instead be a consequence of perseverative responding to the previously relevant dimension. In the 'learned irrelevance' condition, the previously relevant dimension is replaced by a novel dimension and subjects must respond to the previously irrelevant dimension rather than the novel one. Failure to make an attentional shift in this condition must therefore be due to exaggerated 'learned irrelevance' of the previously irrelevant dimension rather than to perseverative responding.

Table 1 *Sample characteristics*

Group	*n*	Age	Estimated IQ
$\{AR^- + CS\}$	25	38.0 (20.0)	112.0 (18.0)
$\{AR^+ + HD\}$	13	34.0 (19.0)	111.0 (14.0)
$\{AR^+\}$	8	34.5 (22.8)	110.5 (12.8)

Data are median (IQR) values. Estimated IQ = IQ estimated from National Adult Reading Test (Nelson, 1982). $\{AR^- + CS\}$ = combined non-Huntington's disease-mutation carrier and control subject group; $\{AR^+ + HD\}$ = combined asymptomatic and symptomatic Huntington's disease mutation carrier group; $\{AR^+\}$ = asymptomatic mutation carriers only.

Statistical analysis

The cognitive data were analysed using the statistical package SPSS V4.0 (SPSS Inc., Chicago, Ill., USA) running on an Apple Macintosh PowerBook 180 computer. As the data were distributed non-normally, the non-parametric Mann–Whitney *U* test was used. Two planned comparisons were made: the first compared all subjects with the Huntington's disease mutation $\{AR^+ + HD\}$ with mutation-negative subjects and control subjects not from Huntington's disease families $\{AR^- + CS\}$. If there was a significant difference between the two groups a second comparison was made. The second comparison compared the AR^+ group alone to the $\{AR^- + CS\}$ group. The first comparison examined the effects of the Huntington's disease mutation on cognition regardless of clinical symptomatology, and the second examined cognitive function in asymptomatic mutation carriers alone. The $AR^?$ subjects were not included in the analyses as their gene status was unknown.

The relationship between selected cognitive variables and striatal dopamine receptor binding was examined using non-parametric Spearman rank correlations. Only data from the Huntington's disease and AR^+ groups were included in the correlation analyses.

Results

Sample characteristics are presented in Table 1. As non-parametric statistical tests were used, data are presented in terms of the median score and interquartile range (IQR; the range of the middle 50% of observations) for each variable of interest (Howell, 1993). A group of 20 control subjects (designated group CS) was included for comparison with the Huntington's disease and AR groups on the cognitive tests. The five symptomatic Huntington's disease subjects were scored on the activities of daily living scale (ADL) of the Unified Huntington's Disease Rating Scale (Huntington Study

Table 2 *Verbal fluency and recognition memory data*

Group	Letter fluency	Semantic fluency	Pattern recognition	Spatial recognition	Pattern latency	Spatial latency
AR^- + CS	38.5 (25.0)	25.5 (15.8)	22.0 (2.5)	17.0 (2.0)	2124.0 (604.5)	2273.0 (637.0)
AR^+ + HD	29.0* (26.5)	17.0** (9.5)	21.0 (3.5)	17.0 (3.5)	2669.0* (1313.5)	2831.0 (1362.5)
AR^+	43.0 (27.3)	18.0* (8.5)	21.5 (1.8)	18.0 (2.8)	2621.0 (1240.8)	2426.5 (978.3)

Data are median (IQR) values. Pattern/spatial recognition = pattern/spatial recognition memory score; pattern/spatial latency = pattern/spatial recognition memory response latency in milliseconds; {AR^- + CS} = combined non-Huntington's disease mutation carrier and control subject group; {AR^+ + HD} = combined asymptomatic and symptomatic Huntington's disease mutation carrier group; {AR^+} = asymptomatic mutation carriers only. *$P < 0.05$; **$P < 0.01$ compared with {AR^- + CS}.

Group, 1996). The median score obtained was 21.0 (IQR 10.0), indicating relatively mild functional impairment.

Calculating estimated number of years to disease onset in AR^+ subjects

The number of years to disease onset was estimated for the AR^+ group using the regression equation provided by Rubinsztein *et al*. (1997): log (age) = a + β(CAG repeat number), where a = 6.15 (SE = 0.095) and β = –0.053 (SE = 0.0021). This model was found by Rubinsztein *et al*. (1997) to account for 69% of the variation in the age of onset of Huntington's disease in a sample of 293 patients.

Estimated years to onset for A/R^+ subjects was computed by subtracting their age from the estimate of age at onset calculated using the above regression equation.

The median CAG repeat length in the A/R^+ subjects was 45.0 (IQR 1.75), the median estimated age at onset was 43.0 (IQR 4.75), and the median estimated years to onset was 8.0 (IQR 18.5).

Cognitive tests

Verbal fluency

Letter fluency. The combined Huntington's disease gene carrier group {AR^+ + HD} performed significantly less well than the non-carrier group {AR^- + CS} on letter fluency [$U(36) = 77.5$, $P < 0.02$]. The asymptomatic AR^+ group alone, however, were unimpaired relative to controls [$U(31) = 57.5$, $P = 0.09$].

Semantic fluency. The combined {AR^+ + HD} group performed significantly less well than non-carriers {AR^- + CS} on semantic fluency [$U(36) = 68.5$, $P < 0.01$]. Asymptomatic AR^+ subjects also performed significantly less well than non-carriers [$U(31) = 46.0$, $P = 0.03$]. Data are presented in Table 2.

Pattern and spatial recognition memory

Pattern recognition. The {AR^+ + HD} group were not impaired on pattern recognition memory compared with the {AR^- + CS} group [$U(36) = 109.0$, $P = 0.13$]. They were, however, significantly slower to respond [$U(36) = 84.0$, $P = 0.02$]; this was not the case for the AR^+ group [$U(31) = 63.0$, $P = 0.12$].

Spatial recognition memory. {AR^+ + HD} subjects were not impaired relative to {AR^- + CS} subjects on spatial recognition memory [$U(36) = 153.5$, $P = 0.94$], although they showed a trend towards slower responses [$U(36) = 97.0$, $P = 0.06$]. Data are presented in Table 2.

Visual discrimination learning/attentional set-shifting

The main index of performance was errors to criterion at the EDS stage. Performance at earlier stages of the task did not differ between the two groups (data not shown). A total ED_{error} score was calculated by summing errors over the EDS and EDR stages.

Perseveration condition. The combined {AR^+ + HD} group made no more errors in reaching criterion than the {AR^- + CS} group [$U(36) = 117.0$, $P = 0.36$], neither were they slower to respond at the EDS stage [$U(36) = 104.5$, $P = 0.18$].

Learned irrelevance condition. The {AR^+ + HD} group made no more errors in reaching criterion than the {AR^- + CS} group [$U(36) = 111.5$, $P = 0.34$], neither were they slower to respond at the EDS stage [$U(36) = 101.0$, $P = 0.35$]. Data are presented in Table 3.

Spatial span

The combined {AR^+ + HD} group had significantly shorter span lengths than did the non-carrier {AR^- + CS} group [$U(36) = 57.0$, $P = 0.002$]. In addition, the AR^+ group alone also had significantly shorter spans than did non-carriers [$U(31) = 46.5$, $P = 0.03$]. Data are presented in Table 4.

Spatial working memory

The {AR^+ + HD} group did not make significantly more between-search errors than the {AR^- + CS} group [$U(36) = 104.5$, $P = 0.10$]: they also made similar use of a search

Table 3 *Visual discrimination learning/set-shifting data*

Group	Perseveration ED_{errors}	Learned irrelevance ED_{errors}	Perseveration ED latencies (s)	Learned irrelevance ED latency (s)
{AR^- + CS}	4.0 (4.5)	2.0 (1.0)	1.21 (0.86)	1.35 (1.33)
{AR^+ + HD}	4.5 (7.0)	3.0 (10.8)	1.50 (1.17)	1.26 (0.48)
{AR^+}	4.5 (7.0)	2.0 (6.5)	1.64 (1.04)	1.31 (0.63)

Data represent median (IQR) values. {AR^- + CS} = combined non-Huntington's disease mutation carrier and control subject group; {AR^+ + HD} = combined asymptomatic and symptomatic Huntington's disease mutation carrier group; {AR^+} = asymptomatic mutation carriers only.

Table 4 *Spatial span, spatial working memory and Tower of London data*

Group	Spatial span	Swm bs errors	Swm strategy	TOL perfect	TOL attempts	TOL LFR (s)
AR^- + CS	6.0 (3.0)	17.0 (21.0)	32.0 (10.0)	18.0 (3.5)	22.0 (3.5)	15.25 (8.62)
AR^+ + HD	5.0** (1.0)	30.0 (23.0)	29.0 (11.5)	15.0** (5.5)	27.0** (9.5)	11.39 (7.56)
AR^+	5.0* (1.5)	25.5 (27.8)	28.5 (12.5)	16.0* (4.3)	26.0* (5.5)	10.30 (4.98)

Data represent median (IQR) values. Swm bs errors = spatial working memory between search errors; TOL perfect = Tower of London first-time correct solutions; TOL attempts = total responses required over all Tower of London problems; TOL LFR = latency of first responses on Tower of London; {AR^- + CS} = combined non-Huntington's disease mutation carrier and control subject group; {AR^+ + HD} = combined asymptomatic and symptomatic Huntington's disease mutation carrier group; {AR^+} = asymptomatic mutation carriers only. *$P < 0.05$; **$P < 0.01$ compared with {AR^- + CS}.

strategy as non-carriers [$U(36) = 151.5$, $P = 0.89$]. Within-search errors were negligible in both groups and not amenable to statistical analysis. Data are presented in Table 4.

One-touch Tower of London

Three main performance measures were made. The first was the number of 'perfect solutions', that is the number of problems (maximum = 20) solved correctly on the first response. The second was the total number of responses made during the task (minimum = 20). The final measure was the latency for the first response on each problem, regardless of whether or not the response was correct. This gives a measure of response latencies uncontaminated by performance accuracy.

In terms of the number of perfect solutions, the {AR^+ + HD} group made significantly fewer first-time correct solutions than the {AR^- + CS} group [$U(36) = 65.5$, $P = 0.007$], as did the AR^+ group alone [$U(31) = 51.5$, $P = 0.04$]. The {AR^+ + HD} group also required significantly more responses to solve the 20 problems overall, compared with the {AR^- + CS} group [$U(36) = 60.0$, $P = 0.007$], as did the AR^+ group alone [$U(31) = 45.0$, $P = 0.02$]. The {AR^+ + HD} group were no slower to respond than the {AR^- + CS} group [$U(36) = 115.0$, $P = 0.33$]. Data are presented in Table 4.

Sequence generation

Four main performance measures were calculated. The number of correct responses (maximum = 24) on phases 1 and 2 (i.e. pre- and post-training) was calculated. In addition, for phase 1 a 'sequence span' score was calculated, by summing the number of consecutively correct spans from trial 1 until a sequence was repeated. Finally, a 'strategy acquisition' score was calculated in the following way: a strategy score was calculated for both phase 1 and phase 2 of the task by calculating the number of 'blocks' in which subjects made five or more sequences beginning with the same box (maximum = 4). Strategy scores in phase 1 were subtracted from strategy scores in phase 2 to give a measure of how effectively subjects had acquired the optimal performance strategy presented in the training phase of the task.

Phase 1. The {AR^+ + HD} group were able to generate as many novel sequences as the {AR^- + CS} group [$U(36) = 118.0$, $P = 0.29$], and the two groups had comparable sequence span lengths [$U(36) = 122.5$, $P = 0.59$].

Phase 2. The {AR^+ + HD} group generated significantly fewer sequences than did the {AR^- + CS} group [$U(36) = 62.0$, $P = 0.007$], as did the AR^+ group alone [$U(31) = 49.0$, $P = 0.04$].

Strategy score. The {AR^+ + HD} group were somewhat less efficient in their acquisition of the optimal performance strategy than the {AR^- + CS} group [$U(36) = 93.0$, $P < 0.10$], but the difference did not reach significance. Data are presented in Table 5.

Correlation analysis

Non-parametric Spearman's rank correlations were used to examine the relationship between selected cognitive variables

Table 5 *Sequence generation task data*

Group	Phase 1 score	Phase 2 score	Sequence span	Strategy score
{AR^- + CS}	17.0 (3.0)	23.0 (5.5)	8.5 (7.0)	1.50 (3.8)
{AR^+ + HD}	16.0 (3.5)	17.5 (5.5)**	6.5 (6.5)	0.5 (2.0)
{AR^+}	16.0 (2.3)	18.5 (5.3)*	6.5 (5.0)	0.5 (2.5)

Data represent median (IQR) values. {AR^- + CS} = combined non-Huntington's disease mutation carrier and control subject group; {AR^+ + HD} = combined asymptomatic and symptomatic Huntington's disease mutation carrier group; {AR^+} = asymptomatic mutation carriers only. *$P < 0.05$; **$P < 0.01$ compared with {AR^- + CS}.

Table 6 *Spearman's rank correlation coefficients between cognitive performance and dopamine receptor binding potentials*

	Caudate D_1	Putamen D_1	Caudate D_2	Putamen D_2
Letter fluency	–0.28	–0.10	0.47*	0.59*
Pattern recognition latency	–0.14	–0.37	–0.67**	–0.72**
Spatial span	0.71**	0.56*	0.72**	0.61*
TOL perfect solutions	0.03	–0.24	0.61*	0.61**
TOL total attempts	–0.11	0.14	–0.67**	–0.68**
Sequence generation, phase 2	0.60*	0.30	0.67**	0.60*

TOL perfect solutions = Tower of London first-time correct solutions; TOL total attempts = total responses required over all Tower of London problems. *$P < 0.05$; **$P < 0.01$.

Table 7 *Intercorrelations between dopamine ligand binding potentials*

	r_s	P
D_1 caudate versus D_1 putamen	0.89	<0.001
D_2 caudate versus D_2 putamen	0.95	<0.001
D_1 caudate versus D_2 caudate	0.90	<0.001
D_1 putamen versus D_2 putamen	0.76	0.006

and striatal dopamine receptor binding. To reduce the number of statistical comparisons, only those test measures sensitive to the presence of the Huntington's disease mutation were examined. Correlation coefficients between cognitive measures and PET binding measures are presented in Table 6. Intercorrelations between the PET measures are given in Table 7. Correlations between CAG repeat length and dopamine ligand binding potentials were not made, as data were only available for the AR^+ subjects, and Weeks *et al*. (1996) reported no correlations between CAG repeat expansion size and binding potentials in these subjects. Likewise, correlations were not made between ADL scores and binding potentials, given the small number of observations (five).

Caudate D_1 binding correlated with performance on spatial span and sequence generation phase 2. Putamen D_1 binding correlated with spatial span. Caudate D_2 and putamen D_2 binding correlated with letter fluency, pattern recognition latencies, spatial span, the Tower of London task and sequence generation phase 2 (Table 6).

An additional analysis was carried out to examine the relationship between estimated years to onset in the AR^+ group and receptor binding levels and cognitive performance, using Spearman's rank correlation coefficient. There were significant correlations between the estimated number of years to onset and caudate D_1 ($r_s = 0.89$, $P < 0.01$), putamen D_1 ($r_s = 0.71$, $P = 0.05$), caudate D_2 ($r_s = 0.94$, $P < 0.01$) and putamen D_2 ($r_s = 0.89$, $P < 0.01$) binding potentials. There were also significant correlations between estimated years to onset and pattern recognition latencies ($r_s = –0.71$, $P = 0.05$) and spatial recognition scores ($r_s = 0.88$, $P = 0.01$). Several other correlations between estimated years to onset and cognitive scores approached significance ($P < 0.1$). Thus, as might be expected, striatal DA receptor levels and cognitive performance decline as AR^+ subjects approach their estimated age of onset of clinical symptoms.

Discussion

In this study we have shown evidence that Huntington's disease mutation carriers perform less well than subjects not carrying the Huntington's disease mutation on a number of neuropsychological tests and that performance on several of these tests correlates with PET measures of striatal dopaminergic receptor binding.

The group of Huntington's disease mutation carriers {AR^+ + HD} performed significantly less well than non-carriers on tests of letter and semantic verbal fluency, had significantly increased latencies on a pattern recognition memory test, had reduced spatial spans, made significantly fewer perfect solutions and required more choices overall to complete the Tower of London problems, and generated significantly fewer novel sequences on phase 2 (i.e. post-training) on the sequence generation task. In addition, the asymptomatic gene carrier group alone were impaired on the above measures with the exception of letter fluency and pattern recognition response latencies. This study failed to show an effect on an attentional set-shifting task, unlike a parallel study with another group of preclinical Huntington's disease patients (Lawrence, 1997).

However, this may be attributable to the use of a different (easier) form of the task in this study and a smaller sample size.

Each of the tests sensitive to preclinical Huntington's disease has previously been shown to be sensitive to symptomatic Huntington's disease (Butters *et al*., 1978; Rosser and Hodges, 1994; Lange *et al*., 1995; Lawrence *et al*., 1996; Lawrence, 1997). What is especially significant about the pattern of these results is that it reflects not merely the effects of task difficulty or sensitivity but rather the breakdown of specific cognitive processes that are essential to performance on certain tasks. All the tasks on which Huntington's disease mutation carriers show an impairment require the optimal timing and generation of motor responses and the serial ordering of responses into their correct temporospatial sequence, as opposed to simple choice behaviour, suggesting a role for the striatum in the optimization of action and the sequential organization of behaviour, consistent with current theories of the functions of the basal ganglia (e.g. Robbins and Brown, 1990; Graybiel *et al*. 1994; Rolls, 1994; Brooks, 1995; Berns and Sejnowski, 1996; Mink, 1996).

The results of the verbal fluency tasks are broadly in line with the Huntington's disease literature (e.g. Butters *et al*., 1978; Rosser and Hodges, 1994). Jason *et al*. (1988) and Blackmore *et al.* (1995) have previously found unimpaired performance of AR^+ subjects on letter fluency tasks, as is the case in the present study.

In this study, however, semantic verbal fluency was impaired in asymptomatic mutation carriers. It is unlikely that the differences in semantic verbal fluency are a result of IQ differences between the two groups, as the mean IQ levels of the two groups were similar. Although semantic verbal fluency is considered to be less 'effortful' than letter fluency (Martin *et al*., 1994), Barr and Brandt (1996) have reported that semantic verbal fluency is relatively more impaired than letter fluency in Huntington's disease patients, irrespective of dementia severity, and a recent functional neuroimaging study (Cardebat *et al*., 1996) found activation in the right dorsolateral prefrontal cortex during the performance of a semantic task but not a letter fluency task. The authors suggested that this frontal activation reflects the use of semantic categorization strategies in semantic fluency. It may be that the AR^+ group are less able to use categorization strategies to improve their performance on the fluency task, and as a result have impaired scores compared with subjects not carrying the Huntington's disease mutation. Certainly, it has been reported that both symptomatic (Delis *et al*., 1991) and asymptomatic (Rosenberg *et al*., 1995) Huntington's disease mutation carriers are deficient in their use of semantic organization strategies on verbal learning tasks. Performance on letter but not semantic verbal fluency correlated with levels of caudate and putamen dopamine D_2 binding. This suggests that impaired letter fluency is related to striatal dysfunction.

Short-term pattern and spatial recognition memory was unimpaired in both symptomatic and asymptomatic mutation carriers. This is in contrast to the results from a larger sample of early-stage symptomatic Huntington's disease patients (Lawrence *et al*., 1996) and probably reflects the relative preponderance of preclinical subjects in the present study. However, symptomatic Huntington's disease mutation carriers did show significantly prolonged response latencies on the pattern recognition task compared with non-Huntington's disease subjects, and these response latencies correlated significantly with measures of caudate and putamen D_2 binding.

These results fit in well with single-unit recording studies in the striatum of behaving animals. Nishino *et al*. (1984) report neurons that fire in the striatum in relation to motor responses coupled to the presentation of visual objects, such as food items. The magnitude of these neuronal responses was inversely correlated with response latencies. Rolls (1994) reports neurons in the striatum that fire in relation to response initiation to a visual stimulus in a delayed matching-to-sample task. These results suggest that the striatum is involved in preparing/initiating responses to visual objects.

The spatial span lengths of both the $\{AR^+ + HD\}$ group and AR^+ subjects alone were significantly shorter than those of non-mutation carriers. We have previously shown spatial spans to be reduced in early stage Huntington's disease patients (Lawrence *et al*., 1996). Further, in the latter study span lengths correlated significantly with motor screening latencies, suggesting that reduced spans may also be associated with impaired motor sequencing.

Spatial span performance correlated with levels of both caudate and putamen D_1 and D_2 binding. This is in line with other evidence suggesting that the striatum is involved in movement sequencing. L-dopa withdrawal in Parkinson's disease results in a reduction in spatial span (Lange *et al*., 1992). PET imaging studies in humans (Boecker *et al*., 1996) and neurophysiological recording studies in behaving monkeys (Kermadi and Joseph, 1995) have found activity in the basal ganglia during the performance of spatial sequencing tasks, consistent with the proposal of a role for the striatum in the sequencing of responses. In Huntington's disease patients, Bradshaw *et al*. (1992) have reported that symptomatic Huntington's disease patients and some at-risk subjects performed poorly on a task requiring sequential button presses, also in line with the present findings.

Both the $\{AR^+ + HD\}$ and the AR^+ groups were impaired on phase 2 but not phase 1 of the sequence generation task, and performance on phase 2 of the sequence generation task correlated significantly with caudate D_1 and caudate and putamen D_2 binding levels. There are at least two plausible explanations for the finding that the AR^+ subjects are impaired only on phase 2 of the sequence generation task. One possibility is that the prefrontal cortex is involved in the initial phase of the task, when the self-generation of a novel task schema is required (Owen *et al*., 1995), whereas in the second phase of the task performance has become more 'automatic' and its control is devolved to the striatum.

Certainly, patients with Huntington's disease have been shown to be impaired in certain tasks requiring only 'automatic' processing (Strauss *et al*., 1985). Alternatively, it may be that the AR^+ subjects do not implement a strategy used by control subjects to improve performance on the second phase of the task. Statistical analysis revealed that there was a trend towards a significant difference between groups in terms of this strategy measure, suggesting that inability to implement an optimal task performance strategy may in part be the cause of impairment on phase 2 of the sequence generation task. Impairments in strategy generation on this task have been found in patients with frontal lobe lesions and Parkinson's disease (J. L. Iddon, R. Swainson, B. J. Sahakian, J. R. Hodges, B. A. Summers, C. E. Polkey, T. W. Robbins, unpublished findings), and this is also the case for patients with clinically symptomatic Huntington's disease (Lawrence, 1997), suggesting that both symptomatic and asymptomatic Huntington's disease mutation carriers may be unable to use organizational strategies to the same extent as non-carriers of the mutation, in order to optimize performance. The present data indicate that this is especially the case for visuospatial functions, but may also apply to verbal semantic tasks.

Performance on tests of planning has not previously been assessed in subjects at risk for Huntington's disease prior to the work reported here, although Rosenberg *et al.* (1995) have found that AR^+ and AR^- subjects did not differ on the Tower of Toronto test, which bears some resemblance to the Tower of London test of planning. However, solutions to the Tower of Toronto can be edited 'on-line' and thus this test is not as stringent a test of 'look ahead' planning as the Tower of London (Goel and Grafman, 1995). In the current study, accuracy of planning was impaired in both the {AR^+ + HD} and the AR^+ group. Both symptomatic and asymptomatic mutation carriers made significantly fewer first-time correct solutions and required more attempts overall to solve the Tower of London problems. The Tower of London taps higher-order 'executive processes' thought to be dependent upon the functions of the prefrontal cortex, and recent functional neuroimaging studies have found significant activations in the prefrontal cortex when subjects perform these tasks, in particular in the dorsolateral and rostral prefrontal cortex together with regions of the parietal cortex (Baker *et al*., 1996).

In this study, performance on the Tower of London test correlated significantly with striatal dopamine receptor binding levels. Both the number of first-time correct solutions and the overall number of choices required to solve all task problems correlated significantly with caudate and putamen D_2 binding levels. Further, non-medicated Parkinson's disease patients, but not medicated patients, are impaired in terms of planning accuracy on the Tower of London test (Lange *et al*., 1992; Owen *et al*., 1995), suggesting a relationship between planning ability and striatal dopaminergic status. The dorsolateral prefrontal cortex and posterior parietal cortices project mainly to adjacent, longitudinal domains of the anterior striatum, although there is also evidence for limited convergence of prefrontal and parietal cortical input within the striatum, particularly in the anteriormost part of the head of the caudate nucleus (Selemon and Goldman-Rakic, 1985), and these pathways are thought to constitute an anatomical circuit mediating spatial memory (Levy *et al*., 1997).

The spatial span, the Tower of London test and sequence generation tasks all require the serial ordering of responses into the correct spatiotemporal sequence and performance on all tasks correlated with levels of striatal dopamine receptor binding. These data thus support the hypothesis that the basal ganglia are involved in the sequencing of actions (e.g. Dominey, 1995; Berns and Sejnowski, 1996). Overall, the present results are consistent with the only other studies to look at the relationship between dopamine receptor binding in the striatum and cognitive function in Huntington's disease. Brandt *et al*. (1990) reported correlations between binding of the D_2 ligand [^{11}C]methylspiperone in the striatum and performance on the Trail-Making and Symbol Digit Modalities tests in Huntington's disease, both of which require the rapid execution of responses and the serial ordering of stimuli. Very recently, Backman *et al*. (1997) reported correlations between caudate and putamen D_1 and D_2 binding and dopamine transporter density, and performance on tests in which the correct serial ordering of responses and the rate at which information can be processed/retrieved are critical (symbol–digit substitution, verbal fluency, Tower of Hanoi test and Trail-Making test), in a small sample of Huntington's disease patients.

The basal ganglia presumably form only part of a neural system that controls response sequencing. Neurophysiological studies in humans and monkeys suggest that areas of the frontal lobe including the premotor cortex and supplementary motor area also play a role in the sequencing of actions (Jenkins *et al*., 1994; Sadato *et al*., 1996; Shima *et al*., 1996; Tanji, 1996), as do output nuclei of the striatum, such as the globus pallidus (Mushiake and Strick, 1995). The supplementary motor area projects via the motor cortex to the lateral putamen and dorsolateral caudate, which in turn projects via the globus pallidus and ventral anterior thalamus back to the supplementary motor area (Strick *et al*., 1995; Inase *et al*., 1996), thus forming one of the parallel re-entrant corticobasal ganglion thalamocortical loops linking the basal ganglia and frontal cortex (Alexander *et al*., 1986), and may act in parallel to sequence response output (Romo and Schultz, 1992).

More generally, from a functional perspective the basal ganglia should not be viewed in isolation. It makes better sense to attempt to ascribe behavioural functions to entire circuits of interconnected neural structures than to individual structures themselves (Alexander *et al*., 1992). The basal ganglia receive topographic projections from all areas of the cortex, and in turn project their own influences back upon areas of the frontal and temporal lobes via topographically organized pathways that pass through the thalamus

(Alexander *et al*., 1986; Middleton and Strick, 1996). The basal ganglia should be viewed as components of circuits organized in parallel and remaining largely segregated from one another (Strick *et al*., 1995).

In this study, cognitive performance correlated with both D_1 and D_2 receptor binding levels, but mainly with D_2 binding levels, even though D_1 and D_2 binding potentials were themselves highly correlated. This suggests that D_1 and D_2 receptor-bearing neurons might subserve different roles in cognition. However, given the relatively small number of subjects in the present study, it is far too early to draw any firm conclusions in this area.

There is considerable controversy regarding whether or not D_1 and D_2 receptor subtypes are expressed by distinct subpopulations of medium-sized spiny neurons in the striatum. Recent studies have only added to the confusion in this area. Gerfen *et al*. (1995) and Hersch *et al*. (1995) report that D_1 and D_2 receptors are expressed on different populations of striatal neurons, D_1 receptors being mainly expressed on neurons in the 'direct' pathway, and D_2 receptors on neurons in the 'indirect' pathway. However, Surmeier *et al*. (1996) have reported that D_1 and D_2 class receptors are co-localized in ~50% of all medium spiny projection neurons.

In humans it has also been suggested that D_1 neurons are found preferentially in striosomes, whereas D_2 neurons predominate in the matrix component of the striatum (Joyce *et al*., 1986), but in the monkey Rappaport *et al.* (1993) found a rather more complex distribution, D_1 receptors being concentrated in striosomes in the caudate, with a more homogeneous distribution of D_1 receptors throughout the putamen. D_2 receptors showed no preferential expression in striosomes or matrix in either caudate or putamen. It is not yet known whether prefrontal cortical regions project differentially to D_1 and D_2 mRNA-containing neurons, but a significantly higher proportion of motor cortex neurons synapse with D_1- rather than D_2-containing striatal neurons, at least in the rat (Hersch *et al*., 1995).

In addition to providing insights into the functions of the striatum, these results further suggest that dysfunction of the striatum occurs in Huntington's disease mutation carriers prior to any overt signs of the disease, consistent with the hypothesis of preclinical neuronal loss in Huntington's disease (Myers *et al*., 1991). Whether this represents a loss of function of the normal huntingtin protein, which may be important for striatal development (Nasir *et al*., 1995), or subclinical excitotoxic damage resulting from some action of the mutant Huntington's disease protein (Bhide *et al*., 1996), is unknown.

In conclusion, we have shown that cognitive impairments are present in Huntington's disease mutation carriers prior to the onset of overt clinical symptoms. In the case of tasks requiring the optimal scheduling and sequencing of responses, this deficit in performance could be related to loss of dopamine receptor binding in the striatum in symptomatic and asymptomatic carriers of the Huntington's disease mutation. These findings thus suggest a specific role for the striatum, as part of a complex neuronal architecture interlinking the prefrontal cortex and the basal ganglia, in the cognitive dysfunction seen in Huntington's disease.

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