Cognitive deficits in Huntington’s disease are predicted by dopaminergic PET markers and brain volumes

L. Bäckman,1,2,3 T.-B. Robins-Wahlin,2,3 A. Lundin,4 N. Ginovart4 and L. Farde4

1Department of Psychology, Göteborg University, Göteborg, 2Stockholm Gerontology Research Centre, 3Department of Clinical Neuroscience and Family Medicine, Section of Geriatrics, Karolinska Institute and 4Department of Clinical Neuroscience, Section of Psychiatry, Karolinska Institute, Stockholm, Sweden

Correspondence to: Lars Bäckman, Stockholm Gerontology Research Center, Olivecronas väg 4, S-113 82 Stockholm, Sweden

Summary
The main aim of this study was to investigate the relationship between dopaminergic markers and brain volumes for striatal and cortical structures, and cognitive performance in patients with Huntington’s disease and control subjects. We used PET and MRI data as predictors of performance in tasks assessing executive function, visuospatial ability, episodic memory, verbal fluency, perceptual speed and reasoning. The dopamine neurotransmission parameters (D1 and D2 receptor density and dopamine transporter density) and the volumetric measurements for caudate and putamen accounted for substantial portions of the variance across the majority of cognitive tasks. In addition, frontal volume showed a strong relationship with all cognitive tasks. D1 binding and volume measurements for the temporal cortex and thalamic volume showed associations with a select number of cognitive tasks. The overall data pattern is consistent with the view that Huntington’s disease may be characterized as a frontostriatal dementia, in which cognitive deficits may result from pathological changes at multiple sites in the frontostriatal circuitry.

Keywords: Huntington’s disease; cognition; dopaminergic markers; PET; MRI

Abbreviations: ANOVA = analysis of variance; DAT = dopamine transporter; R-OCF = Rey–Osterrieth’s Complex Figure; TMT = Trail Making Test; WCST = Wisconsin Card Sorting Test

Introduction
Huntington’s disease is a progressive, neurodegenerative disorder with a typical clinical onset between 30 and 50 years of age. The clinical manifestations of Huntington’s disease involve prominent motor dysfunction and cognitive deterioration, as well as psychiatric symptoms and personality changes (for reviews, see Brandt and Butters, 1986; Brown and Marsden, 1988). Huntington’s disease-related deficits have been reported in tasks assessing a variety of cognitive skills, including episodic memory (Caine et al., 1977; Butters et al., 1978; Moses et al., 1981), executive functions and mental flexibility (Boll et al., 1974; Josiassen et al., 1983; Taylor and Hansotia, 1983; Butters et al., 1985), visuospatial ability (Fedio et al., 1979; Mayeux et al., 1983; Brouwers et al., 1984; Mohr et al., 1991; Filoteo et al., 1995), procedural learning (Fedio et al., 1979; Martone et al., 1984) and verbal fluency (Butters et al., 1978; Wexler, 1979; Tröster et al., 1989; Rosser and Hodges, 1994). Importantly, processing speed is a central component in many of the tasks described above. Thus, the observed patterns of results are consistent with the notion that Huntington’s disease is characterized by a reduction in mental tempo (Brandt and Butters, 1986; Brown and Marsden, 1988).

It is of interest to relate the cognitive deterioration to the specific neuropathology in Huntington’s disease. The neuropathology is characterized by a loss of medium spiny neurons, the predominant neuronal population in the striatum (Graveland et al., 1985; Goto et al., 1989). A more recent observation is that frontal gyri become atrophic along with
the striatum (Webb and Trzepacz, 1987; Jernigan et al., 1991). The striatum is densely innervated by dopaminergic fibres and contains a high density of postsynaptic D1 and D2 receptors, which are located on the medium spiny neurons (Seeman et al., 1993; Hall et al., 1994). D1 is the predominant dopamine receptor in the neocortex (Murray et al., 1990; Giros et al., 1992), and may thus serve as a marker for the presynaptic neuron. Post-mortem examinations and in vivo studies with PET have demonstrated marked reductions of D1 and D2 receptors in the striatum of Huntington’s disease patients (Hägglund et al., 1987; Filloux et al., 1990; Richfield et al., 1991; Sedvall et al., 1994; Turjanski et al., 1995). Moreover, a recent PET study demonstrated loss of D1 receptors in the frontal cortex of Huntington’s disease patients (Sedvall et al., 1994). Biochemical research indicates a Huntington’s disease-related dysfunction in the presynaptic dopamine neurons that ascend from the midbrain (Ferrante and Kowall, 1987). The dopamine transporter (DAT) is a protein located presynaptically on dopaminergic nerve terminals (Kuhar et al., 1990; Giros et al., 1992), and may thus serve as a marker for the presynaptic neuron.

In a recent PET and MRI study of Huntington’s disease patients, we found a parallel reduction of D1 and D2 receptor binding sites in the striatum. These reductions were related to the duration of the illness (Ginovart et al., 1997). The density of D1 receptors was also reduced in the temporal cortex, but not in the frontal cortex. In addition, a Huntington’s disease-related reduction of DAT was found in the caudate and putamen. The MRI assessment showed striatal atrophy, along with reduced volumes of the frontal cortex and thalamus (see Table 1).

Striatal regions are topographically organized with abundant reciprocal connections to the neocortex (Graybiel and Ragsdall, 1979; Crosson, 1992) and thalamus (Dom et al., 1976; Jayarman, 1984). There is substantial evidence that the basal ganglia serve a key function in integrating information through cortico-striato-thalamocortical circuits (Bryan et al., 1979; Gerfen, 1989; Parent, 1990). Thus, given the Huntington’s disease-related degeneration of the striatal nuclei, as well as their projections to cortical and subcortical areas (Bryan et al., 1979; Graveland et al., 1985; Alexander et al., 1986; Reiner et al., 1988; Goto et al., 1989; Parent and Hazrati, 1995), widespread effects on cognitive functions are to be expected in this disease. Attempts at linking the subcortical and cortical changes in Huntington’s disease with cognitive performance and functional ability have been relatively successful. Relationships between CT-based measures of caudate atrophy and indices of both functional and cognitive ability have been reported (Shoulson et al., 1982; Sax et al., 1983; Starkstein et al., 1988). Bamford et al. (1989) found strong associations between CT measures of striatal and frontal atrophy and cognitive test performance in a group of early-stage Huntington’s disease patients. Starkstein et al. (1992) observed that MRI-based measures of caudate and frontal atrophy correlated with a factor indexing memory and speed of processing in mild to moderate Huntington’s disease patients, although no relationships were found with measures of putaminal or thalamic atrophy. Brandt et al. (1995) recently reported that an MRI-based measure of left caudate atrophy was related to memory for item and contextual information in mild to moderate Huntington’s disease patients; no reliable relationships with measures of other basal ganglia structures were obtained. In another recent report, Harris et al. (1996) found a somewhat different outcome. In their study, Huntington’s disease-related deficits in various cognitive tasks (i.e. visual and verbal episodic memory, Trail Making and Stroop tests) were related to volumetric measurements of both caudate and putamen. In addition, measures of regional cerebral blood flow in caudate, putamen and thalamus were related to measures of cognitive ability.

### Table 1

<table>
<thead>
<tr>
<th>Structure</th>
<th>Volume (mm³)</th>
<th>D₁</th>
<th>D₂</th>
<th>DAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington's disease</td>
<td>Control subjects</td>
<td>Huntington's disease</td>
<td>Control subjects</td>
<td>Huntington's disease</td>
</tr>
<tr>
<td>Caudate</td>
<td>2065.20</td>
<td>3834.20</td>
<td>0.67</td>
<td>1.13</td>
</tr>
<tr>
<td>Putamen</td>
<td>603.67</td>
<td>672.92</td>
<td>0.28</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean</td>
<td>3447.60</td>
<td>5361.80</td>
<td>0.84</td>
<td>1.28</td>
</tr>
<tr>
<td>SD</td>
<td>396.98</td>
<td>885.58</td>
<td>0.30</td>
<td>0.17</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>14835.20</td>
<td>18190.60</td>
<td>0.31</td>
<td>0.30</td>
</tr>
<tr>
<td>SD</td>
<td>1590.65</td>
<td>726.53</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>13482.40</td>
<td>16138.40</td>
<td>0.35</td>
<td>0.46</td>
</tr>
<tr>
<td>SD</td>
<td>1574.05</td>
<td>2136.66</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Thalamus</td>
<td>4832.60</td>
<td>5965.20</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SD</td>
<td>624.01</td>
<td>607.65</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Adapted from Ginovart et al. (1997). *Values represent the means of both hemispheres because no significant asymmetry was observed.

---

L. Backman et al.

---

2208
pet and cognition in Huntington's disease 2209

putamen and thalamus, derived from single photon emission computed tomography, correlated with performance in several of the cognitive tasks. Interestingly, the best overall predictor of cognitive performance was a global measure of atrophy, namely the percentage of cerebrospinal fluid volume in the whole brain. These results suggest a more global influence of an impaired cortico-striato-thalamocortical system on Huntington's disease-related cognitive deficits than has been implied in prior research.

The present investigation represents an extension of the PET and MRI study reported by Ginovart et al. (1997) (see Table 1). The main aim was to explore the relationship between dopamine neurotransmission parameters and cognitive performance in Huntington's disease patients and normal control subjects. To our knowledge, this is the first attempt to relate dopaminergic PET markers to cognitive functioning in Huntington's disease. An additional purpose was to relate volumetric MRI measurements to cognitive performance. In this way, potential differences between the neurotransmitter parameters and volumetric measurements with regard to the effects on cognitive functioning could be determined. The cognitive battery was designed to tap a wide variety of cognitive domains known to be implicated in Huntington's disease. The battery involved tests of executive function, visuospatial ability, episodic memory, verbal fluency, perceptual speed, and reasoning. Although we expected a general relationship between the biological and cognitive variables, a final objective was to examine the relative predictive power of the biological indices for performance in the respective cognitive tests.

Method

Subjects

Five patients with Huntington's disease (three men and two women) and five healthy control subjects (three men and two women) were included in the study. The subjects gave informed consent after the nature and possible consequences of the study were described, and the study was approved by the Ethics and Radiation Safety Committees of The Karolinska Hospital, Stockholm. The groups were matched on age and educational background. The Huntington’s disease group had a mean age (± SD) of 49.4 ± 7.6 years and had completed an average of 11.5 ± 1.5 years of formal education. The control subjects had a mean age of 48.0 ± 7.8 years and averaged 11.9 ± 0.7 years of schooling. The clinical diagnosis of Huntington's disease was based on the presence of the typical motor and cognitive symptoms in patients with a family history of Huntington's disease. The diagnosis was confirmed by molecular genetic analysis showing a CAG repeat length of >37 in the gene locus for Huntington’s disease. The exact number of CAG repeats was, however, not known to any of the investigators, according to the Huntington Study Group policy on non-disclosure of CAG trinucleotide repeat length. The duration of illness varied between 2 and 8 years (mean ± SD = 5.6 ± 2.5 years). Exclusion criteria for the control subjects included history of mental disorder, significant somatic condition, abnormal MRI and current or previous abuse of drugs or alcohol. No subject was on medication, and subjects were not allowed to drink any alcohol during 48 h prior to the testing.

The Huntington’s disease patients had a mean Mini-Mental State Examination (Folstein et al., 1975) score of 25.8 ± 1.3, indicating a mild to moderate global cognitive impairment. One Huntington’s disease patient had depressive symptoms at the time of the investigation.

MRI and PET assessment

A detailed description of the MRI and PET assessment was provided by Ginovart et al. (1997). Briefly, a head fixation system was used which allowed transfer of positioning from MRI to PET, and repeated PET assessments with the same positioning of the head (Bergström et al., 1981). MRI examinations were performed using an MR Signa Advantage System (General Electric, Signa 1.5 T) at the Karolinska Hospital, providing 124 contiguous slices of the entire brain with a resolution in the axial plane of 1.5 mm.

PET studies were performed on a Siemens ECAT Exact HR 47 (Wienhard et al., 1994). Each subject participated in three PET measurements performed on the same day. The PET measurements followed the procedure described by Farde et al. (1994, 1995). The radioligands used were [11C]SCH 23390 for D1 receptors, [11C]raclopride for D2 receptors and [11C]β-CIT for DAT (Farde et al., 1986, 1987, 1994, 1995). Regions of interest were drawn manually on the MRI images. The following structures were delineated: caudate (the head), putamen, thalamus, frontal cortex, temporal cortex and cerebellum. The MRI-defined regions of interest were used to calculate structural volumes. The regions of interest drawn on the MRI images were transferred to the corresponding PET images to obtain time curves for regional brain radioactivity.

[11C]SCH 23390 and [11C]raclopride binding to D1 and D2 receptors, respectively, was calculated using a ratio method (Farde et al., 1986, 1995). The cerebellum was used as a reference region for the free radioligand concentration (F), since this region contains negligible densities of D1 and D2 receptors (Hall et al., 1988; Cortés et al., 1989). Specific binding (B) was defined as the total binding in a region of interest reduced by F. The B : F ratio was calculated for each region of interest, providing an index of the density of available receptors (Farde et al., 1986, 1995). [11C]β-CIT was analysed using a multiple-time graphic analysis (Patlak et al., 1983; Patlak and Blasberg, 1985). This analysis provides an influx constant (Ki), which is linearly related to the density of the DAT (Ginovart et al., 1997).

Cognitive testing

The cognitive test battery was administered by an experienced psychometrician (T.-B.R.-W.) at the Stockholm Gerontology
Reseach Centre. Subjects were tested individually. The time elapsed between the brain imaging and the cognitive assessment averaged 1.60 ± 0.89 days for the Huntington’s disease patients and 2.00 ± 2.23 days for the control subjects (\( P > 0.50 \)). The total testing time for the cognitive battery was ~3 h.

The test battery was designed to measure a broad spectrum of cognitive functions, including executive functions [Trail Making Test (TMT), Wisconsin Card Sorting Test (WCST) and Tower of Hanoi], episodic memory [word recall and Rey–Osterreith’s Complex Figure (R-OCF)—memory]; visuospatial ability (Block Design and R-OCF—copy); verbal fluency (Controlled Oral Word Association Test), perceptual speed (Digit Symbol) and reasoning (Picture Arrangement). The respective tests used are described below.

**Picture Arrangement, Block Design and Digit Symbol**

Three tests from the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (Wechsler, 1981) were used: Picture Arrangement, Block Design and Digit Symbol. Standard rules for administration were employed, and the tests were scored according to WAIS-R criteria. The maximum score for Picture Arrangement was 20, for Block Design it was 51 and for Digit Symbol 93.

**Trail Making Test (TMT) A and B**

A version of the TMT from the Halstead–Reitan Battery (Halstead, 1947; Reitan and Davidson, 1974; Reitan, 1979) was given in two parts, A and B. For both parts, subjects were presented with a white sheet of paper on which circles were distributed. In part A, the circles were numbered from 1 to 25 and subjects were asked to draw lines to connect the 25 circles in correct order (i.e. 1–2–3–...–25). In part B, the circles contained numbers from 1 to 13 and letters from A to L. Subjects were instructed to connect the consecutively numbered and alphabetically lettered circles, by alternating between the two sequences (i.e. 1–A–2–B–...–L–13). In both parts, subjects were told to connect the circles as fast as possible. The number of seconds needed to finish each part was registered. The first error observed was immediately pointed out by the examiner, and the subject was required to correct the error. Thereafter, the subject was asked to continue in the proper sequence. From the second error onwards the subject was not corrected. Performance time was unlimited.

**Word recall**

A total of 20 concrete nouns from different taxonomic categories were used. The 20 words were equivalent with respect to visual and tactual imagery, meaningfulness and frequency, as determined from a normative Swedish study (Molander, 1984). The list was presented at a rate of one word every 5 s. Subjects were told to remember as many words as possible for a subsequent free recall test. The words were presented bimodally; that is, they were shown on printed cards consecutively, and simultaneously read aloud by the examiner. Following presentation of the last word in the list, an oral free recall test was given. The recall task was self-paced.

**Controlled Oral Word Association Test**

The Controlled Oral Word Association Test (Benton and Hamsher, 1989) was administered to assess verbal fluency. In this test, subjects are asked to produce as many words as possible beginning with the letters F, A and S, with the exception of proper names, numbers, and words with the same suffix. One minute was allowed for each letter.

**Rey–Osterreith’s Complex Figure**

The R-OCF (Rey, 1941; Osterreith, 1944) was given in two parts: copy and memory. Subjects were given a blank sheet of paper, and another sheet of paper on which the R-OCF was printed. They were instructed to copy the figure as accurately as possible, with no time restrictions. Following completion, the examiner removed both the original and the copied figure. Completion time was recorded. After a retention interval of 4 min during which the Controlled Oral Word Association Test was completed, subjects were again given a blank sheet of paper, and asked to reproduce the R-OCF from memory. Recall was self-paced. The copy and memory tasks of the R-OCF were scored according to standardized criteria (Taylor, 1959; Lezak, 1995). The maximum score for each of these variables was 36.

**The Wisconsin Card Sorting Test**

Subjects were given two packs of 64 cards in the WCST (Berg, 1948; Grant and Berg, 1948; Milner, 1963). One to four instances of each of four symbols in four different colours were printed on each card (e.g. one red triangle, two green stars, three yellow crosses and four blue circles). The subject’s task was to sort the cards according to a principle inferred from the examiner’s responses to the subject’s placement of the cards. The test involved three principles for sorting: colour, symbol or number. The examiner responded only ‘right’ or ‘wrong’ according to the subject’s placement of the card, and did not answer any questions. After 10 consecutive correct placements, the examiner shifted the principle. The test continued until the subject had made six runs of ten correct placements, or when all 128 cards were placed. In the current study, the number of perseverative errors was used as the criterion variable.

**The Tower of Hanoi**

The puzzle of the Tower of Hanoi (Butters et al., 1985) consisted of three pegs, forming a triangle on a plastic square
foot and five circular plastic blocks. The starting peg was positioned next to the subject where all five blocks were arranged, according to size, to form a tower (the smallest block on the top and the largest on the bottom). Subjects were asked to move the blocks as fast as possible from the starting peg to either of the two other pegs, maintaining the tower form. They were allowed to move only one block at a time, and could never place a larger block on the top of a smaller one. A minimum of 31 moves was needed for optimal solution of the task. Completion time was registered.

**Data analysis**

The cognitive data were entered into separate analyses of variance (ANOVAs), with group (Huntington’s disease patients, control subjects) as a between-subjects variable. For each statistically reliable effect, \( \eta^2 \) was calculated to determine the proportion of variance in cognitive performance that was accounted for by group membership.

We used the dopamine parameters and brain volume data initially reported by Ginovart *et al.* (1997) as correlates of cognitive performance. These relationships may best be determined using homogeneous groups, due to potential aggregation bias for combined data. However, examining within-group relationships was not judged to be feasible in the present study, because of the relatively small sample sizes. Thus, in order to maximize statistical power, the data used in the regression analyses were collapsed across group.

To determine the predictive value of the dopamine neurotransmission and morphological data for cognitive performance, we first conducted blockwise hierarchical regression analyses for each structure and cognitive variable. To examine the relative influence of the dopamine and brain volume data on cognitive performance, two sets of regressions were performed for caudate and putamen. In the first set, the \( D_1, D_2 \) and DAT data were entered first in one block, followed by the brain volume data in the second block. In the second set, order of entry between the two blocks was reversed. For frontal and temporal cortex, the same strategy was applied, although only \( D_1 \) and brain volume data were available. Finally, for thalamus, only volume data were available to predict cognitive performance. In additional regression analyses, we investigated the relative importance of the different biological variables for different cognitive tasks, by entering all biological variables in stepwise forward fashion.

**Results**

**Cognitive data**

The performance by Huntington’s disease patients and control subjects in the cognitive tests is shown in Table 2. As can be seen from this table, ANOVAs revealed significant effects favouring the control subjects for 10 of the 11 tests, suggesting a rather global cognitive deficit in the Huntington’s disease group. The only exception to this pattern was word recall, in which the group difference did not approach conventional significance.

**Relationships between brain imaging parameters and cognitive performance**

**Blockwise hierarchical regression analysis**

The outcomes of the analyses of the predictive effects of the caudate and putamen data were identical; when the block involving \( D_1, D_2 \) and DAT was entered first in the equation, it made a significant contribution to all cognitive variables (all \( P < 0.05 \)), except perseverations in the WCST and word recall (all \( P > 0.20 \)). The amount of variance accounted for by this block was considerable, with \( r^2 \)-values ranging from 0.67 to 0.91. The volume data did not add to the amount of explained variance in any instance (all \( P > 0.20 \)). However, when the order of entry of predictors was reversed, the volume data contributed reliably to all cognitive measures (all \( P < 0.05 \)), except word recall, perseverative errors, TMT-A and TMT-B (all \( P > 0.20 \)). The \( r^2 \)-values for the volume data varied between 0.48 and 0.70 across the seven tasks for which the relationship was reliable. In these analyses, there was no significant contribution of the block of dopamine parameters (all \( P > 0.10 \)). This pattern of results can be understood from the fact that there were sizeable correlations among the data on \( D_1, D_2 \) and DAT, and brain volume in both caudate (\( r^2 \)-values ranging from 0.76 to 0.94, all \( P < 0.05 \)) and putamen (\( r^2 \)-values ranging from 0.73 to 0.89, all \( P < 0.05 \)). Thus, once the blocks of dopaminergic markers or volume variables were taken into account, not much variance was left that could be explained by the remaining block. Yet it should be noted that the neurotransmitter parameters accounted for a greater portion of the variance in cognitive performance than the striatal volume variables across all measures. In addition, the neurotransmitter parameters made a contribution to nine cognitive measures, whereas the volume variables were related to seven cognitive measures.

Frontal volume was related to performance in all cognitive tasks, irrespective of whether it was entered before or after \( D_1 \) in frontal cortex (\( r^2 \)-values ranging between 0.50 and 0.80; \( P < 0.05 \)). \( D_1 \) in frontal cortex was unrelated to performance across all measures (\( P > 0.50 \)). Thalamic volume contributed significantly to performance in verbal fluency, R-OCF-copy, R-OCF-memory and Tower of Hanoi (\( r^2 \)-values between 0.41 and 0.54; all \( P < 0.05 \), but not to the remaining cognitive tasks (\( P > 0.20 \)). Finally, when entered first in the equation, \( D_1 \) in temporal cortex made a reliable contribution to performance in Picture Arrangement, TMT-A, TMT-B and the Tower of Hanoi (\( P < 0.05 \), with no explanatory variance added by temporal volume (\( P > 0.10 \)). However, as was true with caudate and putamen, reversal of order of entry between the dopamine and volume measures resulted in the opposite pattern of results, again.
suggesting substantial colinearity between the two types of biological indices.

**Stepwise regression analyses**

After having established that many of the biological variables and, in particular, that the data pertaining to dopamine parameters in caudate and putamen as well as frontal volume were generally related to cognitive performance, we evaluated the relative importance of the biological indices for specific cognitive tasks. To accomplish this goal, we conducted additional regression analyses for each of the cognitive variables. To control for colinearity among the biological variables, both within and between brain areas, all biological variables were entered in stepwise forward fashion. The outcome of the stepwise regressions is shown in Table 3. The general impression from this table is that DAT in putamen and frontal volume were the most important predictors of cognitive performance, with DAT in putamen being the major predictor in six tasks, and frontal volume being the sole predictor in four tasks. The only exception to this pattern was R-OCF-copy, in which the volume measure of putamen emerged as a single predictor of performance.

Although the strong relationships between the biological indices and cognitive performance were largely due to substantial group differences for both sets of variables, positive associations were also seen within groups. Illustrative examples of these relationships are portrayed in Figs 1 and 2. These figures show the relationship between DAT in putamen and Tower of Hanoi and frontal volume and TMT-B, respectively.

**Discussion**

It is well established that Huntington’s disease is associated with specific neuropathology in striatal and neocortical brain regions (Graveland et al., 1985; Ferrante and Kowall, 1987; Webb and Trzepacz, 1987; Goto et al., 1989; Filoux et al., 1990; Jernigan et al., 1991; Richfield et al., 1991) as well as cognitive impairment (Butters et al., 1978; Fedio et al., 1979; Josiassen et al., 1983; Taylor and Hansotia, 1983; Rosser and Hodges, 1994; Lange et al., 1995; Lawrence et al., 1996). In the research reported here, we sought to link the neuropathology of Huntington’s disease to the cognitive deficits that accompany this disease. This was accomplished by examining the relationship of D1, D2 and DAT densities.
PET and cognition in Huntington's disease

Fig. 1 Relationship between DAT in putamen and Tower of Hanoi (completion time) in patients with Huntington's disease (closed squares) and control subjects (open squares).

Fig. 2 Relationship between frontal volume and Trail Making, part B (completion time) in patients with Huntington's disease (closed squares) and control subjects (open squares).

as well as measurements of structural brain volumes (Ginovart et al., 1997) to cognitive performance in Huntington's disease patients and control subjects.

The cognitive data indicated Huntington's disease-related impairments across all domains assessed (i.e., executive function, visuospatial skill, episodic memory, verbal fluency, perceptual speed and reasoning). In fact, with the exception of word recall, all cognitive measures showed statistically reliable differences between Huntington's disease patients and control subjects. However, for word recall, the performance advantage of the control subjects did not approach conventional significance. This pattern of results, indicating a rather global cognitive deficit in mild to moderate stages of Huntington's disease, is in agreement with prior research (for reviews, see Brandt and Butters, 1986; Brown and Marsden, 1988).

There were several intriguing relationships between the neurotransmitter and brain volume measures and cognitive performance. The D1, D2, and DAT data for both caudate and putamen showed strong relationships to all cognitive tasks, except word recall and perseverations in the WCST. Similar relationships were seen between the morphological data for the striatal structures and cognitive performance, although there was no association with the TMT in these analyses. Note that the order of entering the dopamine binding parameters and the volume data determined which type of biological index would show a relationship to cognitive performance. Specifically, when the dopaminergic markers were entered first in the regressions, the volume data made no additional contribution to the cognitive variation. Conversely, when the volume data were entered first, D1, D2, and DAT did not add any explanatory variance. This pattern of results indicates that both the neurotransmitter and volume data may serve as markers of the pathophysiological process that underlies impaired cognitive functioning in Huntington's disease.

Furthermore, the volume of the frontal cortex was strongly related to performance in all 11 cognitive tasks, whereas temporal volume and D1 in temporal cortex were related to performance in four tasks only: Tower of Hanoi, Picture Arrangement, TMT-A, and TMT-B. As with the analysis of the striatal data, order of entry determined, for the temporal cortex, which type of index that would show a reliable relationship with cognitive performance. Finally, thalamic volume was associated with performance in four tasks: R-OCF-copy, R-OCF-memory, verbal fluency, and Tower of Hanoi.

The overall pattern of results indicates that the dopaminergic markers as well as the brain volume data were related to performance in the majority of cognitive tasks employed. Among the biological indices, measures of frontal volume and dopamine binding in the striatum showed the strongest and most consistent relationships with cognitive performance. It is arguable that the cognitive deficits shown by the current Huntington's disease patients are largely attributable to striatal and frontal lesions, given that these patients exhibited marked reductions in dopamine binding in the striatum as well as frontal volume (Ginovart et al., 1997).

Thus, the present results are consistent with the view that Huntington's disease may be characterized as a frontostriatal dementia (Robbins et al., 1994; Lawrence et al., 1996). Whereas the observed relationships between striatal and frontal volumes and cognitive impairment in Huntington's disease replicate prior research (Shoulson et al., 1982; Sax et al., 1983; Starkstein et al., 1988, 1992; Bamford et al., 1989; Brandt et al., 1995), the associations between the dopamine neurotransmission parameters and cognitive performance constitute novel findings.

Although the cognitive data pattern may reflect Huntington's disease-related lesions at several levels of the frontostriatal circuitry (Lawrence et al., 1996), stepwise regression analyses, which controlled for colinearity among
predictor variables, showed that some relationships between the biological and cognitive variables were stronger than others. In particular, DAT in putamen emerged as the most powerful predictor in Digit Symbol, Block Design, Picture Arrangement, Tower of Hanoi, verbal fluency and TMT-A, whereas frontal volume showed the strongest relationship with R-OCF-memory, word recall, TMT-B, and perseverative errors from the WCST. To the extent that the striatum plays a critical role in fast cognitive performance (Cummings, 1986; Brown and Marsden, 1988; Almkvist et al., 1992; Crosson, 1992), it is noteworthy that the rate at which information could be processed or retrieved is extremely important in all tasks that were predicted by the DAT putamen variable.

Of further interest is that both lesion studies (Moscovitch, 1982; Schacter, 1987; Incisa della Rochetta and Milner, 1993; Wheeler et al., 1995) and PET activation research with normal subjects (Squire et al., 1992; Shallice et al., 1994; Tulving et al., 1994; Rugg et al., 1996) indicate a strong frontal involvement in the encoding and subsequent retrieval of information from episodic memory, as assessed in, for example, word recall and R-OCF-memory. Similarly, there is evidence that proficient executive functioning, as assessed in tasks such as the WCST and TMT-B, draws on the integrity of the frontal cortex (Milner, 1963; Weinberger et al., 1986; Janowsky et al., 1989; Segalowitz et al., 1992; Tranel et al., 1994; Nagahama et al., 1996). Although these specific relationships may be theoretically plausible, we would like to caution that (i) the overall pattern of results indicated a relationship between most biological and cognitive variables, and (ii) the sample sizes used to infer these relationships were relatively small. Thus, at present, the safest conclusion is that the current data reflect a general influence of an impaired frontostriatal system on the cognitive deficits that accompany Huntington’s disease. The fact that the present results suggest that lesions at multiple sites in the cortico-striato-thalamocortical circuitry (i.e. caudate, putamen, frontal cortex and thalamus) may be associated with Huntington’s disease-related cognitive impairment should be highlighted.

Finally, it should be noted that the strong relationships between the biological and cognitive variables were largely due to marked group differences for both sets of variables. Unfortunately, the relatively small sample sizes made within-group regressions less meaningful. However, an interesting relationship between the neurotransmitter parameters and brain volumes, on the one hand, and cognitive performance, on the other. Evidence for a relationship between volume measurements of various cortical and subcortical structures and performance on intelligence tests has been reported in healthy adults (Andreasen et al., 1993). Future research should substantiate the current findings both with regard to Huntington’s disease-related effects and potential general effects.

Acknowledgements

We wish to thank the staff of the PET centre at the Karolinska hospital for their assistance. This research was supported by grants from the National Institute of Mental Health (MH41205-8) and the Swedish Medical Research Council (09114) to L.F., the NHR Foundation and Gadelius Minnesfond to A.L., and the Swedish Council for Research in the Humanities and the Social Sciences (F 67/95) to L.B.


Gerfen CR. The neostriatal mosaic: striatal patch-matrix organization is related to cortical lamination. Science 1989; 246: 385–8.


Seeman P, Guan HC, Van Tol HHM, Niznik HB. Low density of dopamine D4 receptors in Parkinson’s, schizophrenia, and control brain striata. Synapse 1993; 14: 247–53.


Received May 22, 1997. Accepted July 21, 1997