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Dopamine D_1 receptor number – a sensitive PET marker for early brain degeneration in Huntington's disease

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Summary. D_1-dopamine receptor binding in the brain was determined by positron emission tomography (PET) in five patients with Huntington's disease, in one asymptomatic gene carrier and in five control subjects. [^{11}C] SCH 23390 was used as the radioligand. Brain morphology was recorded by MRI. The patients who all had a mild to moderate functional impairment showed an almost 50% reduction of putamen volume as well as D_1-dopamine receptor density as compared to the controls. The total D_1-dopamine receptor number in the putamen was reduced by 75% in the patient group. A similar reduction was found for the caudate nucleus. The asymptomatic gene carrier had volume and density values in the lower range of the control subjects. In the frontal neocortex there also tended to be a reduced D_1-dopamine receptor binding in the symptomatic patients. The results indicate that [^{11}C] SCH 23390 binding in combination with MRI can be used as a sensitive marker for early brain degeneration in Huntington's disease. This marker may be useful to monitor the pathophysiological effect of the disease gene and also to follow therapeutic interventions aiming at preventing the degenerative process.

Key words: Huntington's Disease – Brain degeneration – D_1-Dopamine receptors – Positron emission tomography, PET – SCH 23390.

Introduction

Huntington's disease (HD), the dominantly inherited neurodegenerative disorder, is characterized by progressive choreiform movements, dementia and other neuropsychiatric symptoms. The disease appears at the average age of 40 years and progresses over a 10–30-year period before it causes death (Martin and Gusella 1986).

Pathologically, HD is characterized by marked neuronal loss in the caudate nucleus and putamen but few or no cortical abnormalities (Vonsattel et al. 1985). Neuronal populations of the neostriatum have been classified with respect to their cytoarchitectural features and neurochemical contents (Gerfen et al. 1985; Graveland 1985a; Kowall et al. 1987). Morphologically the cell types are termed spiny and aspiny striatal neurons. In the normal neostriatum about 96% of the neuronal population consists of medium-sized spiny neurons. The degenerative process in HD is characterized by an early and severe alteration of the medium-sized spiny projection neurons and their neurochemical markers (Graveland 1985b; Goto et al. 1989) while large- and medium-sized aspiny interneurons are relatively spared (Ferrante et al. 1987; Ferrante et al. 1991).

Dopamine containing nigrostriatal neurons represent one major afferent pathway to the basal ganglia. This afferent influence seems to be mediated predominantly by two subtypes of dopamine receptors, i.e. the D_1 and the D_2 types. The major fraction of the D_1 dopamine receptors appear to be localized to dendrites and somata of medium spiny neurons where the dopamine message is affecting the phosphorylation state of a D_1-dopamine receptor-regulated phosphoprotein, DARPP32 (Walaas et al. 1983; Quimet et al. 1984; Joyce et al. 1988). The relatively selective localization of D_1-dopamine receptors and DARPP32 to striatal medium-sized spiny neurons and the critical role of such neurons in the degenerative process offers the possibility that alterations of D_1-dopamine receptors and DARPP32 may be used as indices of striatal degeneration in HD. Previous post mortem studies in HD indicated an early and marked loss of D_1-dopamine receptors in the brain of such patients (Reisine et al. 1977; Cross and Rosser 1983; Joyce et al. 1988; Filloux et al. 1990; Richfield et al. 1991).

The gene for HD, has recently been localized to the short arm of chromosome 4p 16 (The Huntington's Disease Collaborative Research Group 1993). Children to carries of the gene have a 50% risk to develop the disease. DNA analysis should give a high reliability for the diagnosis. To follow the pathophysiological effect of the HD gene there is a need for specific in vivo techniques. A sensitive technique for recording of the degenerative process

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in HD may also be useful for evaluating treatment programmes aiming to prevent the degenerative process.

Previously, imaging by computerized tomography (CT), nuclear magnetic resonance (MRI), positron emission tomography (PET), and single photon emission tomography (SPECT), have been used as indicators of degeneration of the neostriatum in HD in early and advanced stages (Leenders et al. 1986; Hayden et al. 1987; Hägglund et al. 1987; Mazziotta et al. 1987; Berent et al. 1988; Brandt et al. 1990; Harris et al. 1992; Hasselbach et al. 1992). In the present study, we examined the possibility to use D_1-dopamine receptor density as a specific PET index for the degeneration process and disease manifestation in HD. The selective D_1-dopamine receptor antagonist [^{11}C] SCH 23390 was used as the PET ligand (Sedvall et al. 1986).

Material and methods

The study was approved by the Ethics and Radiation Safety Committees of the Karolinska Hospital, Stockholm. The subjects included were all given detailed information about the PET investigations and chose to participate after having given informed consent.

As control subjects five male volunteers were recruited. They were all healthy according to medical history, physical examination, blood and urinary tests.

Five patients with a clinical diagnosis of HD and one asymptomatic gene carrier were recruited. Motor signs were present in all symptomatic cases, and date of onset was estimated with regard to when motor signs had been noticed by patient or informant (spouse, parent or close friend) (Table 1).

Besides the neurological symptoms the subjects were healthy according to physical examination and urinary and blood tests. Psychiatric symptoms were not assessed systematically but none of the patients had prominent psychiatric symptoms at the time of the investigation. One of the patients (IA) had mild depression as the first symptom. Another patient(CR) had a short period of generalized anxiety in 1989. He was successfully treated with haloperidol and he was still on medication at the time of the study (0.5 mg b.i.d). The other four patients had a drug-free period for at least 2 weeks before the PET.

Quantified Neurological Examination (QNE) was performed and presented in three subscales, according to Folstein et al. (1983).

MIS	(Motor Impairment Scale)	Maximum score 28.
CS	(Chroea Scale)	Maximum score 25.
EMS	(Eye Movement Scale)	Maximum score 20.

(The maximum score in these scales reflect impairment of function.)

Cognitive function was assessed with the MMSE – Mini Mental State Examination (Folstein et al. 1975). Maximum score 30 (reflecting good function).

Demographic and clinical data for patients and control subjects are presented in Table 1.

Table 1. Demographic and clinical data for human subjects

	Sex	Age (years)	Duration (years)	MIS	CS	EMS	MMSE
HD patients							
ML	male	33	3	7	10	4	22
IA	female	54	2	9	6	4	28
CR	male	61	10	7	10	3	29
SZ	male	40	1	3	5	2	30
GL	female	50	1	7	4	1	27
HD gene carrier							
RH	male	47	0	0	0	0	30
Healthy subjects							
EH	male	31					
AE	male	25					
TB	male	26					
JG	male	26					
JB	male	22					

MIS, Motor Impairment Scale; CS, Chorea Scale; EMS, Eye Movement Scale; MMSE, Mini Mental State Examination

MRI and PET experiments

All the imaging experiments were performed at the PET Center, Karolinska Institute and Hospital, Stockholm. For each subject, an individual plaster helmet was moulded to allow head fixation for MRI and PET experiments. Each helmet was constructed to orient the image plane to the plane defined by the meatus acusticus externus and the lateral angle of the orbita. Before the PET experiment each subject participated in an MRI examination of the brain (Siemens-Magnetom, 1.0 T, sequence of scan SE 23 ms/2 s, plane thickness 4 mm, slice separation 6.5 mm). In order to have the same coordinates in MRI and PET, a calibration box was used for both imaging modalities (Bergström et al. 1981). The measurements from the box determined the positioning of the subject in the positron camera.

Each subject participated in two PET experiments with [^{11}C] SCH 23390. In the first, a high, and in the second, a low specific radioactivity was used. Both experiments were performed on the same day. [^{11}C] SCH 23390 was prepared according to a procedure described in detail by Halldin et al (Halldin et al. 1986). At least 3 hours elapsed between the PET experiments to allow for radioactivity decay. Before the first PET experiment, an arterial cannula was inserted into the brachial artery of the left arm and a venous cannula into the antecubital vein of the right arm. In each PET experiment the subject was placed supine and the head was fixed to the positron camera by the plastic helmet. A Scanditronix PC2048-15B camera was used (Litton et al. 1990). The camera has a resolution of 4.5 mm (FWHM) in the plane and a plane thickness of 6 mm. It measures radioactivity in 15 horizontal planes covering the whole extension of the brain. A transmission scan was performed before each experiment for attenuation correction. The radioligand (193–324 MBq) was injected intravenously as a bolus during 3 s. In experiments with high specific radioactivity, 2–6 μg of [^{11}C] SCH 23390 was injected. In experiments with low specific radioactivity, 0.7–1.0 mg of the compound was used. Regional radioactivity in the brain and arterial blood was measured according to preprogrammed sequences from the time of injection up to 33–57 min.

Calculations

Volume measurements. On the MRI images regions of interest (ROIs) were drawn for the caudate nucleus, the putamen, a frontal neocortical region and the cerebellum (Fig. 1). ROIs for the caudate nucleus and the putamen were drawn on all planes on which they appeared. ROIs for the frontal cortex were drawn on planes where the insula was visible bilaterally. The volume for each ROI was measured from the product of the ROI area and the thickness of the plane. ROIs for the cerebellum were drawn on the most rostral plane where the petrosus bones appeared bilaterally.

PET measurements. The ROIs drawn on the MRI images were transferred to the corresponding PET images for radioactivity and

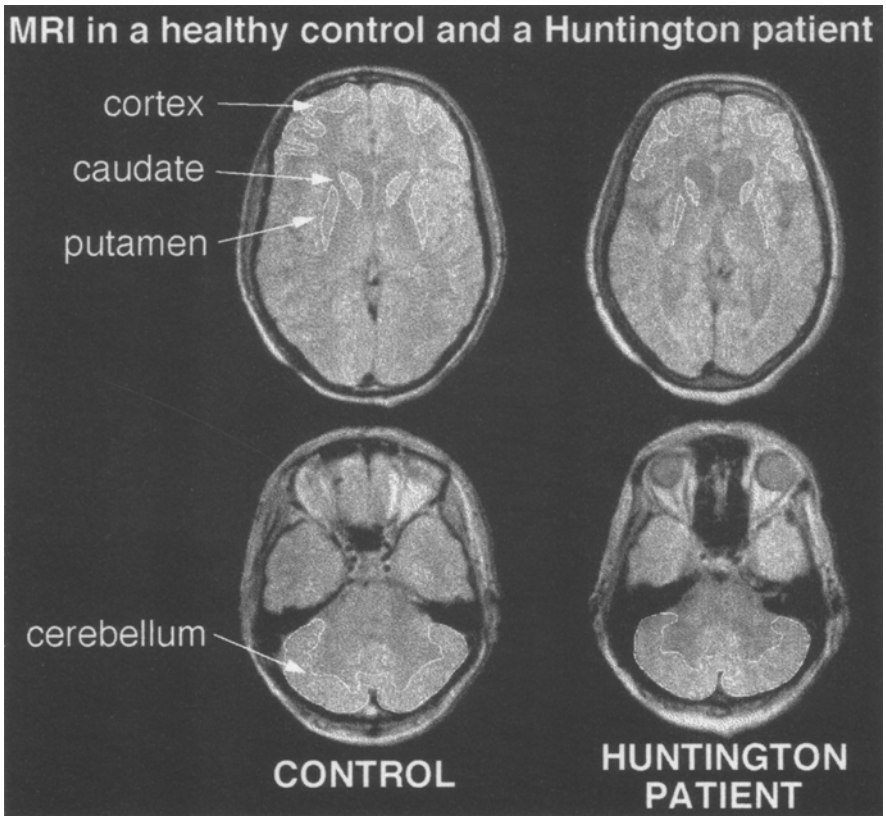

Fig. 1. MRI scan through the level of the basal ganglia and the cerebellum in a healthy control subject (left panel) and a patient (ML) with Huntington's Disease (right panel). Regions of interest (ROIs) are indicated by *white lines*

receptor density measurements. To minimise partial volume effects the ROIs selected for the caudate nucleus and putamen measurements were derived from the two PET planes were radioactivity in these regions was highest. These radioactivity measurements were extrapolated to the entire volume of the caudate and the putamen. For the neocortex the same two planes as for the caudate and the putamen were used and in addition the planes immediately above and below. For the cerebellum the ROIs described above were used.

In order to calculate the total number of D_1-dopamine receptors in the putamen, caudate nucleus and neocortex and their affinity for binding [^{11}C] SCH 23390 a Scatchard analysis was used (Farde et al. 1986; Farde et al. 1987).

The cerebellar cortex is a region with negligible density of D_1-dopamine receptors (Hall et al. 1988; Cortés et al. 1989; Meador-Woodruff et al. 1991). The radioactivity in the cerebellar cortex was therefore used as an estimate of the time curve for free and non-specifically bound radioligand concentration in brain ($C_f(t)$). To validate this assumption the ratio of radioactivity in the cerebellum to blood was calculated for [^{11}C] SCH 23390. In the experiments with low specific radioactivity, there was no effect on this ratio indicating that cerebellar radioactivity is a valid estimate for $C_f(t)$.

The time curve for specific radioligand binding ($C_b(t)$) to D_1-dopamine receptors in the putamen and the cortex was defined as the difference between radioactivity in these regions and $C_f(t)$. A set of three exponential functions was fitted to the radioactivity time curves for $C_f(t)$ and $C_b(t)$ (Farde et al. 1988). Time for equilibrium was defined as the moment when the curve for $C_b(t)$ peaked, i.e. $dC_b/dt = 0$.

The value of C_b (expressed in *n*Ci/ml) obtained at equilibrium was divided with the specific radioactivity (expressed in Ci/mmol) of injected [^{11}C] SCH 23390 to obtain the specifically bound radioligand concentration (B) expressed in *n*mol/L.

The ratio of C_b/C_f obtained at equilibrium was calculated to obtain the ratio of specifically bound and free radioligand concentrations (B/F). The ratio of B/F was plotted versus B for the two experiments and a straight line was drawn through the two points. The receptor density (B_{max}) was defined by the intercept of the line with the abscissa and the affinity constant (K_d) by -1/slope.

For all subjects the B_{max} and K_d for the caudate nucleus, putamen and neocortex were measured in this way. However, in most of the HD chorea patients C_b was already low at the high specific radioactivity. At the low specific radioactivity the C_b was even lower. This made it impossible to quantify B_{max} and K_d independently of each other. Therefore, to calculate the B_{max} values for the patients, only data from the high specific radioactivity experiments was used in combination with the average K_d from the healthy controls.

These calculations are based on the assumption that radioactivity in all brain regions represent unchanged [^{11}C] SCH 23390 and that radiolabeled metabolites formed outside the brain do not pass into the brain to a significant extent during the experiment. This assumption has been validated by metabolite studies (Swahn et al. 1992; Swahn et al. 1993).

Screening for metabolic transformation of [^{11}C] SCH 23390 in relation to the PET experiments was made by the analysis of unchanged [^{11}C] SCH 23390 and its metabolites in plasma (Swahn et al. 1992).

Results

The MRI measurements disclosed marked reductions of neostriatal volumes in the HD patients but not in the asymptomatic gene carrier. Thus, as illustrated in Fig. 1 and Fig. 2 the five symptomatic HD patients had smaller volumes for the putamen than any of the control subjects. Also for the caudate nucleus there was a significant volume reduction. On the other hand, there was no significant reduction in the frontal neocortical region.

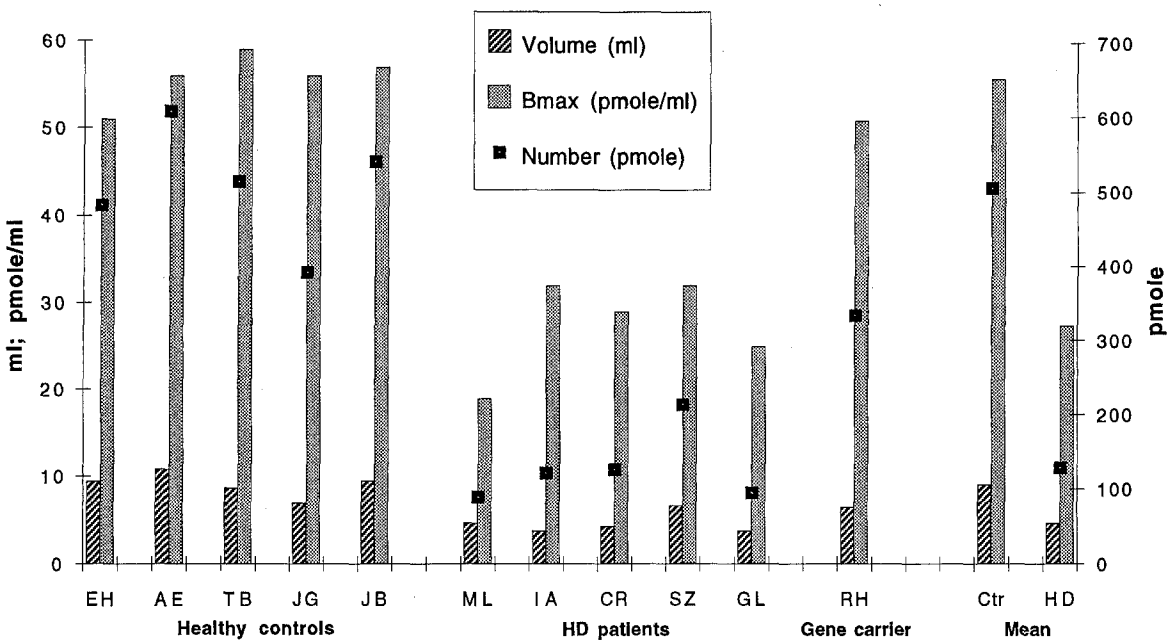

Fig. 2. Volume, D_1-dopamine receptor density and total receptor number of the putamen in five healthy control subjects, five patients with Huntington's Disease and one asymptomatic gene carrier. Data were obtained using MRI and PET with two specific radioactivities (high and low) of the D_1-dopamine receptor ligand [^{11}C] SCH 23390

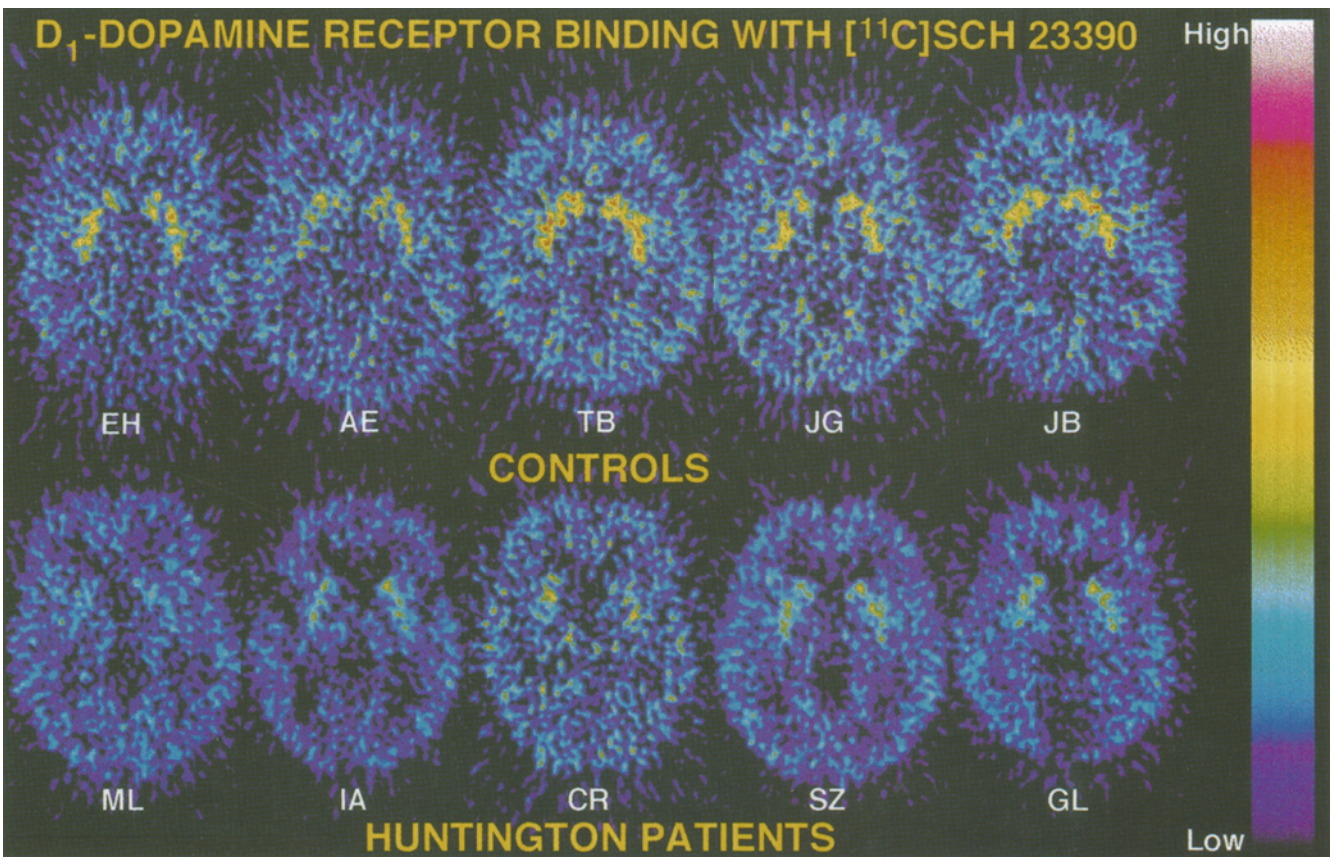

Fig. 3. PET scan images through the plane of the basal ganglia in five healthy control subjects (upper panel) and in five HD patients (lower panel). Images were obtained using high specific radioactivity of the D_1-dopamine receptor ligand [^{11}C] SCH 23390. Images show radioactivity accumulated 15–33 min after injection of the radioligand. Images were normalized with regard to cerebellar radioactivity. Scales indicate the relationship between color and radioactivity.

In the control subjects, the PET analysis demonstrated a high uptake of [^{11}C] SCH 23390 derived radioactivity in the putamen, in the caudate nucleus as well as in neocortical areas (Fig. 3). On the other hand, in all the five symptomatic HD patients, there was markedly lower uptake of radioactivity, predominantly in the putamen and in the caudate but also in the neocortical region. In all the five patients, there was a much lower B_{max} value (i.e. density) of D_1-dopamine receptors in the putamen than in any of the controls (Fig. 2). Since there was a conspicuous reduction of the volume of the basal ganglia in the patients in relation to the controls (Fig. 2), we calculated the total amount of D_1-dopamine receptors within the putamen of each subject. This was made by multiplying the density values by the volume of the region. As shown in Fig. 2 both the density of D_1-dopamine receptors as well as the total number of dopamine D_1-receptors in the putamen of the HD patients was markedly reduced in comparison with the control subjects. If the total number of receptors is taken into account there was a 75% reduction of D_1-dopamine receptors in the putamen of the HD patients as compared to the controls. Similar results were obtained for the caudate nucleus (data not shown). The B_{max} and volume data for the single subject at risk for HD were in the lower range of the values for the control subjects.

Also, in the frontal neocortical region, there appeared to be a reduction of the D_1-dopamine receptor binding in the patients (Fig. 3). However, the relatively low signal in this region made quantitative comparisons unreliable. Furthermore, the volumetric determination of the neocortical region was less reliable due to significant partial volume effects.

There were no significant differences between the total radioactivity levels in the blood or cerebellum in the HD patients as compared to the healthy controls. Neither was there any evidence of alteration of radiotracer metabolism in the two subject groups (data not shown).

Discussion

The localization of D_1-dopamine receptors to medium-sized spiny neurons in the basal ganglia and the critical role of these neurons in the degenerative process in Huntington's disease was the basis for the hypothesis that D_1-dopamine receptors should be markedly reduced in living patients with this disorder. This hypothesis was verified in the present series of HD patients in an early phase of the disease. Thus, the density (B_{max}-value) of D_1-dopamine receptors in the putamen (and also the caudate nucleus) was reduced by about 50% in relation to the control subjects. Since our MRI data – supporting previous MRI studies by Harris et al. (1992) – showed an almost 50% reduction of the putamen volume, our data demonstrate an even more substantial loss of the D_1-dopamine receptor *number* in this brain region. On the average there was a 75% reduction of the D_1-dopamine receptors in the putamen of the HD patients. The two patients with the shortest duration of symptoms (<1 year) had only 42 and 19% of the average receptor number in the control group. Since the patients in this study were slightly older than the control subjects, an age effect may have partly contributed to the marked difference between the subject groups. However, the age effect on D_1-dopamine receptor densities is not very marked before age 40 years and can therefore not account for the present findings (Suhara et al. 1991).

As compared to previous methods for visualizing the degenerative process in living HD patients the present approach may be more sensitive. Previous studies with anatomical imaging techniques, such as computerized tomography and nuclear magnetic resonance, demonstrated an almost 50% reduction of the size of the basal ganglia (Hayden et al. 1987; Harris et al. 1992). PET and SPECT studies of glucose metabolism and blood flow showed a 25–50% reduction of glucose metabolism and flow in early and advanced stages of the disorder (Hasselbach et al. 1992). Dopamine-D_2 receptor binding was examined by PET and found to be reduced in patients with advanced HD (Leenders et al. 1986; Hägglund et al. 1987; Brandt et al. 1990). D_2-dopamine receptors are present predominantly on corticostriatal nerve terminals that do not appear to be primarily affected in HD (Seeman et al. 1987). The D_2-receptor should therefore give a less sensitive signal for the degenerative process in HD as compared to D_1-receptors with their predominant localization to medium-sized spiny neurons. This view is supported by the in vitro studies on brain tissue from diseased HD patients (Reisine et al. 1977; Cross and Rosser 1983; Joyce et al. 1988; Filloux et al. 1990; Richfield et al. 1991).

The present results indicate that determination of D_1-dopamine receptor number by the combination of MRI and PET should be a sensitive in vivo index of the degenerative process in HD. This methodology should be useful for following the brain degeneration and its pathogenetic relationship to the various neuropsychiatric symptoms developing over time as an effect of the HD gene.

Only one asymptomatic gene carrier according to the molecular genetic analysis was examined. This subject showed D_1-dopamine receptor number at the lower range of the healthy volunteers. Thus, our results in this subject did not give support for the view that D_1-dopamine receptor measurements can be used as an independent variable discriminating patients at risk for this disorder.

The low density of D_1-dopamine receptors in the neocortical areas precluded quantitative analysis of D_1-dopamine receptors with the present methods. However, in all of the symptomatic patients the specific D_1-dopamine receptor signal in the frontal cortex was lower than in any one of the healthy control subjects (Fig. 3). These findings suggest involvement of frontal cortical function in this disorder.

Future, more detailed PET and MRI studies of D_1-dopamine receptor binding and anatomy in the basal ganglia, neocortical and other brain regions should be possible using more sensitive high-resolution imaging systems and ligands with higher specific signals. By such a detailed analysis it should be possible to elucidate the functional and neuropsychiatric consequences of graded D_1-dopamine receptor loss in Huntington's disease and its relationship to all the clinical manifestations of this disorder. Such an analysis should be valuable for diagnostic

purposes and in following the effect of treatment interventions when such programmes will be developed.

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