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CORTICAL AND SUBCORTICAL GLUCOSE CONSUMPTION MEASURED BY PET IN PATIENTS WITH HUNTINGTON'S DISEASE

by TORSTEN KUWERT,[1] HERWIG W. LANGE,[2] KARL-JOSEF LANGEN,[1] HANS HERZOG,[1] ALBRECHT AULICH[3] *and* LUDWIG EMIL FEINENDEGEN[1]

(From the [1]Institute of Medicine, Nuclear Research Centre, Jülich, and the Departments of [2]Psychiatry and [3]Neurology, Heinrich-Heine University, Düsseldorf, FRG)

SUMMARY

In 23 patients with moderate to severe Huntington's disease (HD) and 21 normal volunteers, the regional cerebral metabolic rate of glucose consumption (rCMRGlc) was measured in the cerebellum, thalamus, striatum, and cortex using positron emission tomography and the ^{18}F-deoxyglucose method. In contrast to previous reports, rCMRGlc was reduced not only in the striatum, but also in the cerebral cortex of patients with HD as compared with normal subjects. No significant difference between HD patients and normal subjects was found for thalamic and cerebellar rCMRGlc. To investigate the relationship between the clinical status and rCMRGlc, correlation coefficients for the clinical data were calculated for absolute values of rCMRGlc and for cerebellar ratios (CR) of rCMRGlc. The duration of chorea correlated significantly only with the absolute values of frontoparietal and temporo-occipital rCMRGlc and with the CRs of most cortical regions evaluated. The severity of chorea correlated significantly only with lentiform nucleus rCMRGlc. The severity of dementia correlated significantly only with the frontoparietal and temporo-occipital rCMRGlc, the CRs of most cortical regions, and the CR for the caudate nucleus. The degree of disability correlated significantly with the CRs of all regions evaluated except the occipital and the superior frontal cortex. It appears from this study that there is a reduction not only for the striatum but also for cortical rCMRGlc in patients with manifest HD, and that the cortical reduction of rCMRGlc contributes to the severity of clinical symptoms in these patients. This challenges the concept that dementia in HD is of purely subcortical origin.

INTRODUCTION

Huntington's disease (HD) is a rare disorder characterized by autosomal dominant inheritance, chorea and progressive dementia (for a review, *see* Martin and Gusella, 1986; Penney and Young, 1988). As a clinical entity it was first described by Huntington in 1872. At the end of the nineteenth century, two publications independently showed that gross degeneration occurs in the striatum of HD patients (Anton, 1896; Lannois and Paviot, 1897). Since then, numerous reports investigating the neuropathological substrate of HD have been published (for references, *see* McCaughey, 1961; Lange *et al.*, 1976; Vonsattel *et al.*, 1985). In all these, degeneration of the striatum has been described as the most pronounced and typical change in HD. Some authors, however, have clearly stated that, in addition to striatal degeneration, degenerative changes can be found

Correspondence to: Dr T. Kuwert, Institute of Medicine, Nuclear Research Centre Jülich, PO Box 1730, D-5170 Jülich, FRG.

in the cerebral cortex (Alzheimer, 1911; McCaughey, 1961; Lange, 1981). Studies using computerized x-ray tomography (CT) have lent further support to the hypothesis that moderate cortical atrophy can accompany the more pronounced striatal changes in HD (Sax and Menzer, 1977; Terrence *et al.*, 1977; Oepen and Ostertag, 1981; Lange and Aulich, 1986). As cortical involvement in HD is not as pronounced as that of the striatum, and as cortical degeneration has been reported to vary markedly (McCaughey, 1961), its relevance in HD has been questioned (Penney and Young, 1988) and little investigated.

With the advent of positron emission tomography (PET) several authors have measured the regional cerebral metabolic rates for glucose (rCMRGlc) and oxygen ($rCMRO_2$) in HD (Kuhl *et al.*, 1982, 1984*a*; Garnett *et al.*, 1984; Hayden *et al.*, 1986, 1987; Leenders *et al.*, 1986; Young *et al.*, 1986; Hosokawa *et al.*, 1987; Mazziotta *et al.*, 1987; De Volder *et al.*, 1988). Some of these studies have focused on the clinically important issue of early diagnosis of HD and have shown that hypometabolism in the caudate nucleus precedes the onset of clinically overt chorea in persons at risk of HD (Hayden *et al.*, 1986, 1987; Mazziotta *et al.*, 1987). All studies on patients with manifest HD have demonstrated prominent decreases of striatal rCMRGlc and $rCMRO_2$, in agreement with the above-cited neuropathological and CT studies.

So far, only scarce and controversial evidence has existed concerning cortical energy metabolism in HD. Kuhl *et al.* (1982, 1984*a*) did not find a significant decrease of cortical rCMRGlc in their group of 13 patients, although they observed a significant decrease of an anteroposterior ratio of cortical rCMRGlc in a subgroup of 5 patients with a disease duration of more than 6 yrs. Young *et al.* (1986) and Berent *et al.* (1988) stated that in their studies, mainly aimed at investigating the relationship between rCMRGlc and the severity of symptoms in HD, cortical rCMRGlc was normal in their group of 15 patients with early to midstage HD. They related the severity of symptoms exclusively to indices of striatal rCMRGlc. Leenders *et al.* (1986), however, reported a decrease in absolute values of cerebral blood flow, $rCMRO_2$, and rCMRGlc in the frontal cortex of 1 patient with HD. Recently, in a preliminary publication, we described a decrease of cortical rCMRGlc in a group of 13 patients with manifest HD and 5 patients at risk of HD with psychiatric symptoms (Kuwert *et al.*, 1989). This study reports measurements of rCMRGlc in 23 HD patients and 21 normal volunteers using a new-generation high resolution PET scanner. The aims of this study were to compare cortical and subcortical rCMRGlc in patients with manifest HD with the rCMRGlc of normal subjects, and to clarify further the relationship between rCMRGlc and clinical symptoms of this disease with special attention to cortical rCMRGlc.

SUBJECTS AND METHODS

Subjects

Twenty-three patients (mean age 42.7 ± 10 yrs; 12 males, 11 females) with manifest HD and 21 normal subjects (mean age 41.1 ± 12.5 yrs; 15 males, 6 females) entered the study. Both patients and normal subjects were scanned during the same period of time from October 1987 to November 1988. The blood glucose levels at the time of PET examination did not differ significantly between patients and control subjects (4.95 ± 0.67 vs 4.81 ± 0.63 mmol/l glucose). Written and informed consent was obtained from all subjects. The control group consisted of healthy volunteers. None of these individuals had a history of alcoholism, neurological disease, myocardial infarction, or diabetes mellitus and neurological examination was normal. All control subjects were not taking medications.

In the patient group, the diagnosis of manifest HD was made on the basis of a family history of HD and a clinical diagnosis of chorea. Blood tests were performed in these patients to exclude such other extrapyramidal disorders as Wilson's disease and neuroacanthocytosis. Scales ranging from 0 (normal) to 3 (severely disturbed) were employed for grading the severity of clinical symptoms. The severity of chorea was assessed on a clinical rating scale with 0 indicating absence of chorea and 3 indicating the presence of constant or frequent gross choreiform movements (Lange *et al.*, 1983). The degree of dementia was determined using a score derived from a psychometric test battery. Psychometric testing included the vocabulary recognition test MWT-B (Merz *et al.*, 1975; Lehrl, 1977), an abbreviated German version of the WAIS (WIP; Dahl, 1972), a test of visuomotor performance (d2-test; Brickenkamp, 1972), a test measuring attention, concentration, general intelligence and cognitive flexibility (syndrome short test SKT; Erzigkeit, 1977), Benton's test (Benton, 1981), and a German version of Raven's matrices (Raven, 1938; Kratzmeier and Horn, 1980). All single test results were converted into scores ranging from 0 to 3. The average of these scores was defined as the overall degree of dementia. The degree of disability was rated analogously to the Shoulson-Fahn scale (Shoulson and Fahn, 1979; Lange *et al.*, 1983) according to the patients' ability to cope with everyday tasks. Although it was not the aim of this study to correlate rCMRGlc with the type and severity of psychiatric symptoms encountered in HD, it is evident that the presence of severe psychiatric symptoms such as psychosis or depression greatly influences the patient's ability to cope with everyday tasks and that the impact of these symptoms on the patient's condition is also evaluated by the above-described scale.

Table I shows detailed clinical data on the HD patients in this study. The duration of chorea in these patients ranged from 1 to 15 yrs with a mean duration of 6.1 ± 4.1 yrs. The mean severity of chorea was 1.5 ± 0.6, the mean severity of dementia 1.6 ± 0.9, and the mean disability severity 1.4 ± 0.8. Thus patients with both mild and advanced disease were included in this study.

TABLE 1. CLINICAL AND X-RAY CT DATA IN THE GROUP OF PATIENTS WITH HUNTINGTON'S DISEASE

Case	*Age (yrs)*	*Sex*	*DUR (yrs)*	*CHOR*	*DEM*	*DIS*	*Drugs*	*CC/OT*	*Atrophy*
1 (A.B.)	36	M	6	1.5	2.0	1.7	BZ,BA	0.21	1.8
2 (S.B.)	41	F	4	1.5	2.0	1.8	0	0.21	1.5
3 (H.B.)	56	F	7	2.0	1.9	1.4	BA	0.3	1.8
4 (D.B.)	48	F	15	1.5	2.8	2.9	0	0.3	2
5 (M.E.)	31	M	2	2.0	1.1	2.0	PH,BU	0.15	1.2
6 (W.F.)	32	M	1	1.0	0.4	0.4	0	0.14	0.8
7 (K.G.)	35	M	8	0.5	1.7	1.0	BZ	0.1	0
8 (R.H.)	46	F	8	2.0	2.6	1.8	BA	0.18	1
9 (A.K.)	47	M	5	1.5	1.0	0.5	0	0.16	1.3
10 (F.K.)	31	M	5	2.0	1.8	2.0	PH,BU,BZ	0.13	0
11 (U.K.)	46	F	5	1.5	2.5	1.8	BA	0.19	1.8
12 (A.L.)	45	M	1	1.0	2.6	2.0	BA	0.16	1.7
13 (I.M.)	54	F	1	1.0	0.6	0.2	0	0.17	1.5
14 (E.M.)	60	F	10	2.0	2.5	2.4	PH,BU,BA	0.19	1.5
15 (I.O.)	47	F	5	1.0	0.4	0.2	0	0.15	1.2
16 (H.P.)	42	M	10	1.5	2.1	1.0	0	0.18	1.7
17 (G.P.)	33	F	8	1.5	0.7	0.7	0	0.1	1.2
18 (He.P.)	53	F	15	2.5	2.3	2.0	PH	0.19	1.7
19 (K.S.)	32	M	1	0.5	0.2	0.7	0	0.12	1
20 (H.S.)	35	M	5	2.5	1.6	1.0	0	0.14	2
21 (W.S.)	62	M	1	0.5	0	0.7	0	0.13	0.8
22 (G.S.)	27	M	9	2.0	1.0	1.3	0	0.12	1
23 (A.W.)	42	F	9	1.5	2.4	2.0	BZ,PH	0.16	1.7

DUR = duration of chorea; CHOR = severity of chorea; DEM = severity of dementia; DIS = degree of disability; BZ = benzodiazepines; PH = phenothiazines, BU = butyrophenones; BA = substituted benzamides (sulpiride or tiapride); CC/OT = shortest distance between caudate heads/distance between the outer tables of the skull at the CC line; atrophy = cortical atrophy evaluated on CT.

In all patients CT was performed using a CGR ND 8000 head scanner in the same year as the PET study. The control subjects did not have a CT scan. The CT scans were evaluated by a neuroradiologist (A.A.) independently of the clinical and PET data. In order to evaluate caudate atrophy the intercaudate distance (CC) and the distance between the outer tables of the skull (OT) along the CC line were measured (Stober *et al.*, 1984). An index of caudate atrophy was calculated by dividing CC by OT. The mean CC/OT was 0.17 ± 0.05, indicative of caudate atrophy and comparing well with published results for symptomatic HD patients (Stober *et al.*, 1984). Cortical atrophy was evaluated by measuring the width of the three widest sulci in the frontal, parietal, and occipital cortex. Cortical atrophy was then graded from 0 (mean sulcal width <2 mm) to 3 (mean sulcal width >5 mm) as reported elsewhere (Lange and Aulich, 1986). The average degree of cortical atrophy thus evaluated was 1.3 ± 0.6, the degree of parietal atrophy 1.4 ± 0.6. Although no age-matched control group was available for the CT scans, it was concluded that the indices of cortical atrophy given above indicate moderate cortical atrophy in view of the relatively young age of the patients and the fact that postmortem examinations of normal cadavers revealed that no atrophy of the parietal cortex occurs before the age of 60 yrs (Eggers *et al.*, 1984). This interpretation is in good agreement with previous CT studies reporting on moderate cortical atrophy in patients with manifest HD (Sax and Manzer, 1977; Terrence *et al.*, 1977; Oepen and Ostertag, 1981).

Twelve of the 23 HD patients were not receiving medication and 11 were medicated as listed in Table 1. No patient was sedated for the purpose of this study. All patients of this group had refrained from using alcohol at least 1 yr before the PET study.

Positron emission tomography

PET scanning was performed using the Scanditronix PET PC-4096 with a maximal spatial resolution of 4.8 mm in the centre of the field of view and 6 mm in the z axis (full width at half maximum; FWHM). Images were reconstituted by filtered back-projection using a filter width of 5 mm leading to an actual resolution of 7.1 mm in the x and y axes and of 6 mm in the z axis (FWHM). Attenuation-correction was performed using $^{68}Ga/^{68}Ge$ derived transmission scans. The scanning took place in a quiet and dimly lit room, with the subject's eyes open and his ears unplugged. Arterialized blood was drawn through a fine-gauge intravenous cannula. ^{18}F-fluoro-deoxyglucose (FDG) was provided by the Institute of Nuclear Chemistry of the KFA Jülich and synthesized according to the procedure of Hamacher *et al.* (1986), which avoids contamination of FDG with ^{18}F-fluoro-deoxymannose. Cerebral glucose consumption was measured after injection of 5–8 mCi FDG (185–296 MBq) according to the standard procedure described by Reivich *et al.* (1979). rCMRGlc was calculated according to the standard procedure described by Reivich *et al.* (1979) using Sokoloff's model equation (Sokoloff *et al.*, 1977), the kinetic rate constants published by Reivich *et al.* (1985) and a lumped constant of 0.52 (Reivich *et al.*, 1985). In each subject rCMRGlc was measured in 15 orbitomeatal parallel slices (OM slices) simultaneously. The most inferior OM slice was 2.5 cm above the orbitomeatal line.

Data analysis

In order to evaluate cerebellar, thalamic, and cortical rCMRGlc, 21 regions of interest (ROI) were drawn manually by an examiner blind to diagnosis and symptoms of the examined subject (*see* fig. 1). Using a range-setting program provided by the manufacturer of the PET machine, the lowest 20% of the rCMRGlc values were not displayed on the screen allowing the partial volume effect to be minimized by drawing the ROIs close to the peak rCMRGlc of each structure evaluated. The cerebellar, thalamic, and cortical ROIs were identified by comparing the OM-parallel PET slices with anatomical sections of horizontal brain slices (Duara *et al.*, 1983) displayed in a neuroanatomical atlas (Talairach and Tournoux, 1988); the horizontal slices in this atlas can be considered approximately parallel to the OM plane (Szikla *et al.*, 1977). This method takes into account the fact that PET slices obtained at identical levels above an externally defined OM line do not always include corresponding brain regions due to considerable variation between individuals in the size and shape of the head and brain (Talairach and Tournoux, 1988; Duara *et al.*, 1983). As the identification of a single gyrus was thought to be difficult in patients with cortical atrophy, cortical ROIs encompassed several adjacent gyri as described below.

Cortical ROIs were placed on the three following OM-parallel slices. (1) An OM slice corresponding to slice 10 of Talairach's atlas (*see* fig. 1B). On this slice 2 cortical ROIs were drawn on each hemisphere: (a) one on the inferior frontal cortex encompassing the lower parts of the superior, medial and inferior frontal gyri; (b) a second on the inferior (and lateral) temporal cortex encompassing parts of the superior,

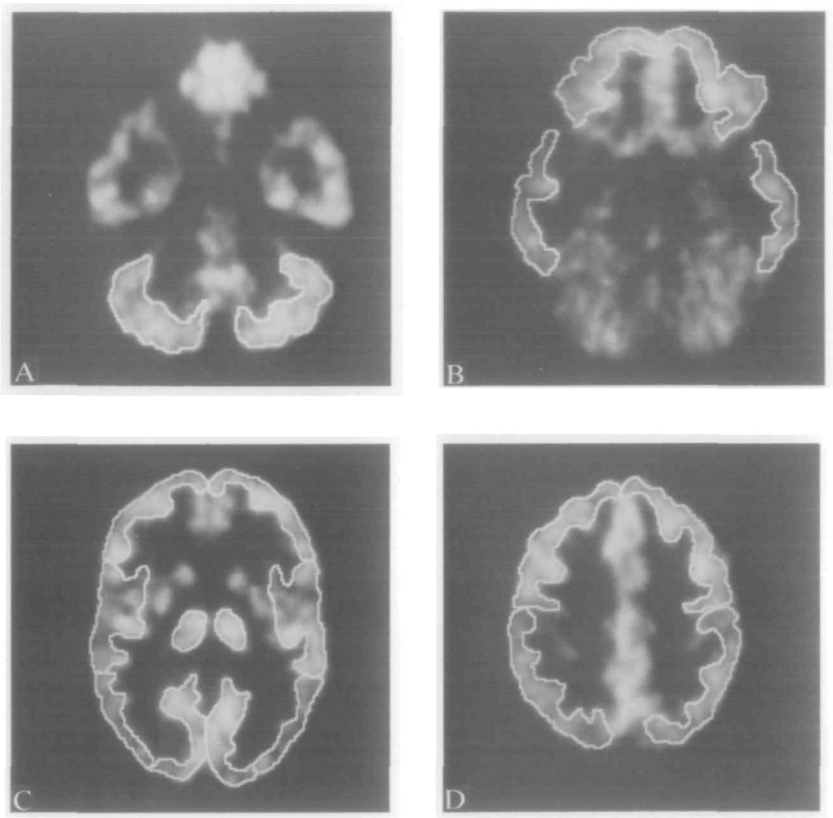

FIG. 1. Regions of interest drawn on orbitomeatal parallel PET slices of rCMRGlc in a normal subject (for description, *see* text).

medial and inferior temporal gyri. (2) An OM slice corresponding to slice 7_8 of Talairach's atlas. On this slice 4 cortical ROIs were drawn on each hemisphere (*see* fig. 1C): (a) one on the intermediate frontal cortex including parts of the superior, medial and inferior frontal gyri; (b) a second on the frontoparietal cortex including parts of the frontoparietal operculum, the insular cortex and a small part of the superior temporal gyrus; (c) a third on the temporo-occipital cortex including parts of the superior and medial temporal gyri, and parts of the medial occipital gyrus; (d) a fourth on the occipital cortex including parts of the medial occipital gyrus, the cuneus and the striate area. (3) An OM slice corresponding to slice 4 of Talairach's atlas. On this slice 2 cortical ROIs were drawn on each hemisphere (*see* fig. 1D): (a) 1 ROI on the superior frontal cortex corresponding approximately to the anterior half of the cortical rim displayed on this slice; (b) 1 ROI on the superior parietal cortex corresponding approximately to the posterior half of the cortical rim displayed on this slice.

Thalamic rCMRGlc was measured by placing a ROI on the thalamus displayed on the PET slice corresponding to Talairach's slices 7_8 (*see* fig. 1C). Cerebellar rCMRGlc was evaluated by placing a ROI on the convolutions of the cerebellar cortex on the PET scan corresponding to Talairach's slices 10_11 (*see* fig. 1A).

An additional ROI comprised the whole brain slice on the OM slice corresponding to Talairach's slices 7_8. Its size can be taken as a relative estimate of the size of the whole brain (Hatazawa *et al.*, 1987*a*).

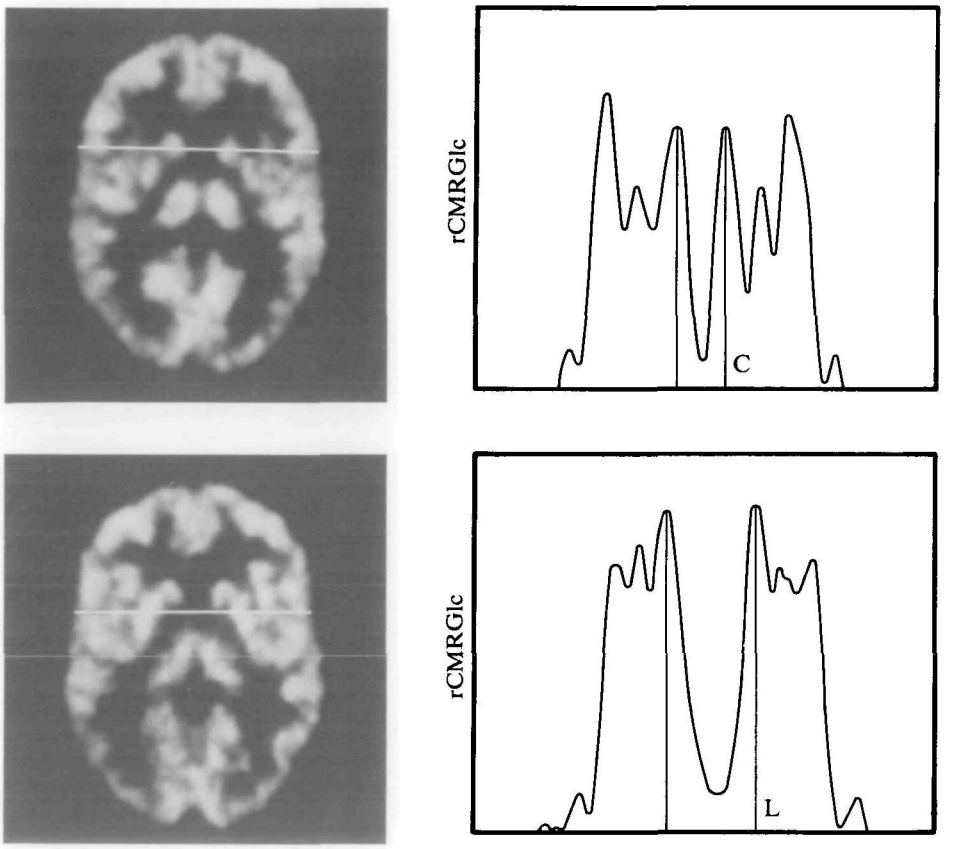

FIG. 2. Cross-sectional histograms were obtained through the caudate heads (*upper*) and through the lentiform nuclei (*lower*), allowing the measurement of caudate (C) and lentiform rCMRGlc (L) (Young *et al.*, 1986).

In addition to the values of rCMRGlc, the ROI sizes were provided by the ROI software of the PET manufacturer. The total cortical ROI area was calculated as the sum of all cortical ROI sizes.

Since in advanced HD, striatal rCMRGlc is low (Kuhl *et al.*, 1982) and the striatum grossly atrophic, visually-guided ROI measurements cannot be considered a precise method for measuring striatal rCMRGlc (Young *et al.*, 1986). In order to overcome this difficulty the method described by Young *et al.* was used to quantify caudate and lentiform rCMRGlc. The principle of this method is that peak values of rCMRGlc are measured on cross-sectional histograms (*see* fig. 2). Using differential range settings, the atrophic caudate nuclei in HD patients were identifiable visually in 21 of 23 cases; in the remaining 2 patients the cross-sectional histograms were placed 1 cm anterior to the anterior tip of the thalamus. The peak value of caudate rCMRGlc was then determined at the shoulder or inflection of the curve, as described by Young *et al.* (1986) and Berent *et al.* (1988). The peak value of the lentiform nucleus was determined analogously on a cross-sectional histogram placed 0.5 cm anterior to the thalamus on the OM-parallel slice corresponding to Talairach's slice 8.

The means of rCMRGlc in the left and right regions (weighted for their cross-sectional area for cortical, thalamic, and cerebellar ROIs) were calculated and used in the further analysis. The arithmetic mean of all cortical regions weighted for their cross-sectional area was calculated as an estimate of the mean cortical glucose consumption of each subject. In order to test Kuhl's hypothesis of hypofrontality in HD patients,

ratios were calculated between the weighted mean of all frontal regions (FRO) and the occipital cortex, between FRO and the weighted mean of the frontoparietal and the superior parietal cortex, and between FRO and the weighted mean of the inferior temporal and the temporo-occipital cortex.

In order to normalize the PET data, cerebellar ratios (CR) were calculated between the value of each region and the cerebellar rCMRGlc in each subject. In order to allow a comparison between this study and the studies by Young *et al.* (1986) and Berent *et al.* (1988), ratios between striatal rCMRGlc and mean cortical rCMRGlc were also calculated (cortical ratios). In addition to an analysis of correlation between the absolute values of rCMRGlc and the clinical data, these cerebellar and cortical ratios were used to correlate PET data with the severity of clinical symptoms because of the great variation of absolute values of rCMRGlc (Kuhl *et al.*, 1982; Tyler *et al.*, 1988).

Statistical analysis was performed using the statistical software package SAS (Statistical Analysis Systems). The difference of group means was tested using Student's t test after correction of the significance level using Bonferroni's correction for each sample. The correlation between PET data and clinical data was performed using Spearman's nonparametric rank correlation coefficients. The level of significance was set at $P < 0.05$.

RESULTS

The surface of the whole slice measured on the PET slice corresponding to Talairach's slices 7_8 was significantly smaller in HD patients than in normal subjects (149 ± 12.5 cm^2 vs 164 ± 8.2 cm^2, $P < 0.01$, Student's t test). Cortical ROI sizes were smaller in HD patients than in control subjects (*see* Table 2); these differences were significant for parts of the frontal and the temporo-occipital cortex.

There was no significant correlation between the total cortical ROI area and rCMRGlc in normal subjects ($r = 0.25$, $P > 0.05$). In HD patients, the correlation coefficient between the total cortical ROI area and rCMRGlc was positive and significant ($r = 0.6$, $P < 0.01$) implying that in those patients in whom larger ROIs were drawn rCMRGlc tended to be higher. The total cortical ROI area correlated negatively with cortical atrophy as determined on CT scan ($r = -0.43$, $P < 0.05$). Mean cortical rCMRGlc correlated negatively with the degree of atrophy as determined on CT scan ($r = -0.58$, $P < 0.01$).

The mean cortical rCMRGlc was significantly reduced in HD patients (*see* Table 3), as was that of caudate and lentiform rCMRGlc. Thalamic rCMRGlc was approximately

TABLE 2. SIZES OF REGIONS OF INTEREST IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23) AND NORMAL SUBJECTS (n = 21)

	HD ROI size (cm^2)	*Normal ROI size (cm^2)*	P[2]
Cerebellum	5.4±0.8[1]	5.6±0.9	n.s.[3]
Thalamus	2.3±0.3	2.4±0.4	n.s.
Inferior frontal cortex	5.9±0.7	6.9±0.9	$P < 0.01$
Intermediate frontal cortex	4.8±0.6	5.7±0.9	$P < 0.01$
Superior frontal cortex	9.0±1.3	10.2±1.5	n.s.
Inferior temporal cortex	4.7±0.9	5.1±1.2	n.s.
Temporo-occipital cortex	4 ±0.8	5 ±0.8	$P < 0.01$
Frontoparietal cortex	11 ±2	12.7±1.8	n.s.
Superior parietal cortex	9.3±1	10.2±1.5	n.s.
Occipital cortex	6.0±0.8	6.4±1	n.s.

[1] Mean ± SD; [2] Two-tailed Student's t test using Bonferroni's correction; [3] Not significant ($P > 0.05$).

TABLE 3. MEAN CORTICAL, SUBCORTICAL AND CEREBELLAR rCMRGlc IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23) AND NORMAL SUBJECTS (n = 21)

	HD rCMRGlc (μmol/100 g/min)	*Normal rCMRGlc (μmol/100 g/min)*	P[2]
Cerebellum	38.2 ± 6[1]	40.3 ± 8	n.s.[3]
Thalamus	44.5 ± 8.1	51.7 ± 10.6	n.s.
Caudate nucleus	21 ± 9.6	55.2 ± 10.3	$P < 0.001$
Lentiform nucleus	28 ± 12.2	63.7 ± 10.9	$P < 0.001$
Mean cortex	38.9 ± 6.6	46.8 ± 8.6	$P < 0.01$

[1] Mean ± SD; [2] Two-tailed Student's t test using Bonferroni's correction; [3] Not significant ($P > 0.05$).

TABLE 4. CORTICAL rCMRGlc IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23) AND NORMAL SUBJECTS (n = 21)

	HD rCMRGlc (μmol/100 g/min)	*Normal rCMRGlc (μmol/100 g/min)*	P[2]
Inferior frontal cortex	38.5 ± 6.4[1]	47.6 ± 9.5	$P < 0.01$
Intermediate frontal cortex	39 ± 7.2	48.1 ± 9.9	$P < 0.01$
Superior frontal cortex	39.6 ± 8.2	48.7 ± 9.5	$P < 0.02$
Inferior temporal cortex	37 ± 7	43 ± 8.3	n.s.[3]
Temporo-occipital cortex	36.3 ± 6.1	42.8 ± 7.5	$P < 0.05$
Frontoparietal cortex	38.3 ± 7.6	46.4 ± 8.7	$P < 0.05$
Superior parietal cortex	38.8 ± 6.6	45.1 ± 8	n.s.
Occipital cortex	45.5 ± 6.2	50.8 ± 9.4	n.s.

[1] Mean ± SD; [2] Two-tailed Student's t test using Bonferroni's correction; [3] $P > 0.05$.

14% smaller in HD patients than in normal subjects; this difference, however, did not reach the required level of significance when Bonferroni's correction was applied. Cerebellar rCMRGlc was only about 5% smaller in HD patients than in normal subjects; the cerebellum thus seemed least affected in this group of HD patients. Significant differences between HD patients and normal subjects were found for rCMRGlc measured in all parts of the frontal cortex, the temporo-occipital cortex, and the frontoparietal cortex (*see* Table 4).

There was no significant difference in rCMRGlc of any brain region between the 12 unmedicated and the 11 medicated patients, implying that the mean cortical rCMRGlc measured in the unmedicated group (38.5 ± 7.3 μmol/100 g/min) also differed significantly from the mean cortical rCMRGlc measured in the control subjects (46.8 ± 8.6 μmol/100 g/min; $P < 0.01$ using the two-tailed Student's t test). This difference between HD patients and normal subjects was also found concerning rCMRGlc measured in the frontal regions: in the 12 unmedicated patients, rCMRGlc was 38.7 ± 7.2 μmol/100 g/min in the inferior frontal cortex (compared with 47.6 ± 9.5 μmol/100 g/min in the control subjects), 39.6 ± 8.6 μmol/100 g/min in the intermediate frontal cortex (compared with 48.1 ± 9.9 μmol/100 g/min in the control subjects), and 38.9 ± 8.5 μmol/100 g/min in the superior frontal cortex (compared with 48.7 ± 9.5 μmol/100 g/min in the normal subjects).

TABLE 5. CORRELATION OF CEREBELLAR, SUBCORTICAL, AND MEAN CORTICAL rCMRGlc WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	Duration of chorea	*Severity of chorea*	*Severity of dementia*	*Degree of disability*
Cerebellum	0[1]	0	0.08	0.26
Thalamus	−0.32	−0.3	−0.18	−0.08
Caudate nucleus	−0.11	−0.31	−0.3	−0.29
Lentiform nucleus	−0.35	−0.43*	−0.34	−0.37
Mean cortex	−0.34	−0.17	−0.3	−0.1

[1] Spearman's correlation coefficients; * $P < 0.05$.

TABLE 6. CORRELATION OF rCMRGlc IN DIFFERENT CORTICAL REGIONS WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	Duration of chorea	*Severity of chorea*	*Severity of dementia*	*Degree of disability*
Inferior frontal cortex	−0.31[1]	−0.15	−0.25	−0.12
Intermediate frontal cortex	−0.33	−0.16	−0.32	−0.15
Superior frontal cortex	−0.35	−0.17	−0.26	−0.04
Inferior temporal cortex	−0.33	−0.18	−0.17	−0.04
Temporo-occipital cortex	−0.51**	−0.3	−0.49*	−0.33
Frontoparietal cortex	−0.42*	−0.24	−0.45*	−0.28
Superior parietal cortex	−0.38	−0.15	−0.28	−0.05
Occipital cortex	−0.35	−0.2	−0.37	−0.08

[1] Spearman's correlation coefficients; * $P < 0.05$; ** $P < 0.02$.

The ratios between the weighted mean of rCMRGlc in the 3 frontal regions and the occipital region (0.86 ± 0.08 as against 0.95 ± 0.1), and between the weighted mean of rCMRGlc in the 3 frontal regions and the weighted mean of the 2 temporal regions (1.06 ± 0.06 vs 1.12 ± 0.07) were found to be significantly decreased in HD patients when calculations using the two-tailed Student's t test and Bonferroni's correction were carried out ($P < 0.05$). The ratio between the weighted mean of rCMRGlc in the 3 frontal regions and the weighted mean of rCMRGlc in the 2 parietal regions was not significantly different in HD patients compared with control subjects (1.02 ± 0.04 vs 1.05 ± 0.05).

The correlation coefficients between absolute values of rCMRGlc and the clinical data are shown in Tables 5 and 6. The severity of chorea showed a significant correlation only with the lentiform rCMRGlc ($P < 0.05$). The duration of chorea and the severity of dementia correlated significantly only with the rCMRGlc in the temporo-occipital and inferior parietal cortex. All other correlation coefficients for absolute values of rCMRGlc and the clinical data were not significant. This was especially true of the correlation coefficients between cerebellar rCMRGlc and the clinical status.

The correlation coefficients between the cortical ratios of striatal rCMRGlc are shown in Table 7. The cortical ratio of lentiform rCMRGlc correlated with the severity of chorea and with the degree of disability at a significance level of 0.05. There was no significant correlation between the cortical ratio of lentiform rCMRGlc and the severity

TABLE 7. CORRELATION OF CORTICAL RATIOS OF STRIATAL rCMRGlc WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	Duration of chorea	*Severity of chorea*	*Severity of dementia*	*Degree of disability*
Caudate nucleus	0.04[1]	−0.23	−0.28	−0.29
Lentiform nucleus	−0.22	−0.42*	−0.32	−0.44*

[1] Spearman's correlation coefficients; * $P < 0.05$.

TABLE 8. CORRELATION OF CEREBELLAR RATIOS OF THALAMIC, STRIATAL, AND MEAN CORTICAL rCMRGlc WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	Duration of chorea	*Severity of chorea*	*Severity of dementia*	*Degree of disability*
Thalamus	−0.4[1]	−0.35	−0.34	−0.51*
Caudate nucleus	−0.09	−0.25	−0.44*	−0.45*
Lentiform nucleus	−0.3	−0.39	−0.4	−0.49*
Mean cortex	−0.48*	−0.14	−0.58**	−0.55**

[1] Spearman's correlation coefficients; * $P < 0.05$; ** $P < 0.01$.

TABLE 9. CORRELATION OF CEREBELLAR RATIOS OF rCMRGlc IN DIFFERENT CORTICAL REGIONS WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	Duration of chorea	*Severity of chorea*	*Severity of dementia*	*Degree of disability*
Inferior frontal cortex	−0.47*[1]	−0.27	−0.5*	−0.62**
Intermediate frontal cortex	−0.34	−0.05	−0.49*	−0.54**
Superior frontal cortex	−0.47*	−0.08	−0.5*	−0.4
Inferior temporal cortex	−0.5*	−0.28	−0.45*	−0.54**
Temporo-occipital cortex	−0.46*	−0.2	−0.59**	−0.66**
Frontoparietal cortex	−0.48*	−0.2	−0.61**	−0.62**
Superior parietal cortex	−0.47*	−0.11	−0.49*	−0.51*
Occipital cortex	−0.3	−0.19	−0.41	−0.4

[1] Spearman's correlation coefficients; * $P < 0.05$; ** $P < 0.01$.

of dementia or the duration of chorea. None of the correlation coefficients between the cortical ratio of caudate rCMRGlc and the severity of symptoms reached the significance level of 0.05.

The correlation coefficients between cerebellar ratios of rCMRGlc and the clinical data are shown in Tables 8 and 9. The duration of chorea correlated significantly with the CR of mean cortical rCMRGlc and with the CRs of rCMRGlc in all cortical regions except the intermediate frontal and occipital cortex. The severity of chorea did not correlate with the CR of any region studied, although the correlation coefficient for the CR of the lentiform nucleus ($r = -0.39$, $P < 0.07$) was almost significant. The severity of dementia correlated significantly with the CRs of the caudate rCMRGlc ($P < 0.05$), of mean cortical rCMRGlc ($P < 0.01$), and of rCMRGlc in all cortical

TABLE 10. CORRELATION OF THE SEVERITY OF CHOREA WITH STRIATAL GLUCOSE CONSUMPTION IN UNMEDICATED PATIENTS WITH HUNTINGTON'S DISEASE (n = 12)

	Caudate rCMRGlc	*Lentiform rCMRGlc*	*Cerebellar ratio of caudate rCMRGlc*	*Cerebellar ratio of lentiform rCMRGlc*	*Cortical ratio of caudate rCMRGlc*	*Cortical ratio of lentiform rCMRGlc*
Severity of chorea	−0.43[1]	−0.36	−0.39	−0.3	−0.39	−0.32

[1] Spearman's correlation coefficients; all correlation coefficients not significant ($P > 0.05$).

regions studied except for the occipital rCMRGlc. The degree of disability correlated significantly with the CR of all cortical regions studied except the superior frontal and the occipital cortex.

The correlation coefficients for the severity of chorea and the absolute values of striatal rCMRGlc and its cerebellar and cortical ratios were of the same magnitude and not significant when the medicated patients were eliminated from the analysis (*see* Table 10).

DISCUSSION

In this study rCMRGlc was measured in a group of HD patients and normal subjects using the well-established standardized method introduced by Phelps *et al.* (1979) and Reivich *et al.* (1979). Various important limitations apply to this method and have been described elsewhere (for reviews, *see* Mazziotta and Phelps, 1986; Sokoloff, 1986). Several points of criticism concerning this method, however, need discussion. In this study arterialized venous blood was used in order to provide data for the plasma input curve into the brain. This method is widely used in PET studies because of its easy feasibility and noninvasiveness. Some criticism of its accuracy has been raised (Budinger *et al.*, 1985). This criticism, however, applies mainly to studies calculating rCMRGlc using FDG rate constants measured in the individual patient, and not to the procedure used in this study where standard rate constants were used. Moreover, a recent study by Tyler *et al.* (1988) has not reported significant differences between rCMRGlc values calculated using arterialized venous blood and those using arterial blood measured in two groups of normal volunteers.

An important limitation of measuring rCMRGlc in grey matter structures is a consequence of the partial volume effect leading to a mixture of grey matter, white matter, and cerebrospinal fluid (CSF) space in each ROI (Hoffman *et al.*, 1979). The partial volume effect influences rCMRGlc values measured in HD patients to a greater extent than those in normal subjects because HD patients have moderate cortical and severe striatal atrophy. This also applies to thalamic rCMRGlc, as thalamic atrophy occurs in some patients with HD (McCaughey, 1961); the ventrolateral thalamus may lose up to 50% of its microneurons (Dom *et al.*, 1976). In this study the partial volume effect is probably less important than in previous ones due to the improved spatial resolution of the PET scanner used (Mazziotta *et al.*, 1981). By using cross-sectional histograms as described by Young *et al.* (1986) to measure striatal rCMRGlc and by drawing the cortical and thalamic ROIs close to the peak values of these structures, additional efforts were made to minimize the partial volume effect. In HD patients,

the total cortical ROI area correlated negatively with the cortical atrophy evaluated on x-ray CT, implying that in patients with more severe cortical atrophy smaller cortical ROIs were drawn, presumably due to shrinkage of the brain in HD patients as described in neuropathological studies (*e.g.*, Lange, 1981). Despite these efforts to minimize the partial volume effect, mean cortical rCMRGlc correlated significantly and negatively with the degree of cortical atrophy as determined on CT scan, indicating that in HD patients a decrease in rCMRGlc parallels the development of cortical atrophy to some extent.

The underestimation of rCMRGlc per mass unit of tissue due to the partial volume effect is a problem inherent in many PET studies comparing rCMRGlc in patients suffering from neurodegenerative diseases such as Alzheimer's disease (AD) with rCMRGlc measured in normal subjects. Controversial results have been reported in the literature. Some authors could clearly show that a correction of PET data for atrophy led to the expected increase of rCMRGlc in AD patients which was more pronounced in AD patients than in normal subjects because of the greater severity of brain atrophy in the AD group (Herscovitch *et al.*, 1986; Chawluk *et al.*, 1987). Preliminary data by Koeppe *et al.* (1989) indicate that—at least in AD patients—the observed decrease of cortical rCMRGlc cannot be ascribed to the influence of cortical atrophy alone. Decreases of rCMRGlc observed in patients with neurodegenerative diseases probably represent a combined effect of cell loss leading to atrophy, disturbed energy metabolism of single neurons, and functional inactivation due to malfunction of neurally interconnected brain regions leading to a loss of activating input. Even if a decrease in rCMRGlc were exclusively caused by inclusion of more white matter or CSF space into the region of grey matter due to atrophy and the partial volume effect, this would not affect the interpretation of a decrease of rCMRGlc as a malfunction of this region (caused predominantly by cell loss).

The principal finding of this study is that in HD patients cortical rCMRGlc is significantly reduced as compared with normal subjects in terms of absolute values. The group of HD patients was older by 1 yr than the group of normal subjects. Although the majority of studies have not found a significant decrease of rCMRGlc with age (e.g., Duara *et al.*, 1983; de Leon *et al.*, 1984, 1987), some authors state the contrary (Kuhl *et al.*, 1984*b*; Riege *et al.*, 1985; Yoshii *et al.*, 1988). The magnitude of these age-related changes, however, is not sufficient to explain a difference of approximately 17% in cortical rCMRGlc between two groups whose mean ages differ by only 1 yr.

The surface of the whole slice ROI placed on the PET slice corresponding to Talairach's slice 7−8 can be assumed to provide a relative measure of brain size (Hatazawa *et al.*, 1987*a*) and was smaller in HD patients than in normal subjects. The group of HD patients comprised more females than the group of normal subjects. These two conditions (smaller brain size, female sex) have been reported to be associated with higher rCMRGlc so that the decreased values found in HD patients are not due to different composition of both groups with regard to these conditions (Baxter *et al.*, 1987; Hatazawa *et al.*, 1987*a*,*b*; Yoshii *et al.*, 1988).

In this study, as in many others (e.g., Duara *et al.*, 1983; Goffinet *et al.*, 1989), a subjective ROI method was used. The cortical ROI sizes in HD patients, however, were smaller than those in normal subjects, and there was no negative correlation between the total cortical surface area analysed and mean cortical rCMRGlc. This indicates that

the difference in mean cortical rCMRGlc between both groups was not caused by erroneously drawing larger ROIs in the HD patients than in the normal subjects.

The data reported in this study suggest that cortical rCMRGlc is most markedly reduced in the frontal cortex and thus confirm the significant decrease of an anterior/posterior ratio as reported by Kuhl *et al.* (1982). This study, however, is the first to report a significant decrease of cortical rCMRGlc in terms of absolute values in a large group of HD patients. The decrease of cortical rCMRGlc was approximately 17%, and thus not as marked as the decrease observed for the striatum. This could possibly explain the failure of previous authors (Kuhl *et al.*, 1982, 1984*a*; Young *et al.*, 1986; Berent *et al.*, 1988) to detect this difference since the PET scanners used in those studies had a lower resolution than the high-resolution PET PC-4096 used in this study (11 to 16 mm vs 4.8 mm); the partial volume effect which increases with decreased spatial resolution (Mazziotta *et al.*, 1981) might have masked this difference.

Another possible explanation of discrepant results reported in previous studies are differences in patient selection: as mean cortical rCMRGlc normalized to the cerebellum correlates negatively with the duration of chorea (*see* Table 8), studies enrolling patients at an early stage of the disease (Young *et al.*, 1986; Berent *et al.*, 1988) will not detect a decrease of cortical rCMRGlc in HD patients.

The finding of decreased rCMRGlc in the cortex is in good agreement with previous neuropathological studies demonstrating cortical cell loss and consecutive brain atrophy in this group of patients (Alzheimer, 1911; McCaughey, 1961; Lange, 1981). The presence of advanced cortical cell loss in patients with HD was further confirmed by studies with x-ray CT revealing the presence of cortical atrophy in these patients (Sax *et al.*, 1983; Terrence *et al.*, 1977; Oepen and Ostertag, 1981). In view of this evidence and the presence of moderate cortical atrophy diagnosed by CT in the HD patients studied, the decrease of cortical rCMRGlc is probably mainly related to direct cortical pathology and not to functional inactivation. As the cortex and the striatum are, however, jointly involved in at least two neuronal circuits (the principal striatal circuit and the fourth 'accessory' striatal circuit according to Nieuwenhuys *et al.*, 1988), a contribution of functional inactivation to the observed decrease of cortical rCMRGlc cannot be excluded completely. Moreover, Laplane *et al.* (1989) have recently described the occurrence of relative prefrontal hypometabolism in patients with lesions involving the lentiform nuclei, which they ascribed to a process of deafferentation of the prefrontal cortex. This lends support to the hypothesis that the observed decrease of the frontal rCMRGlc is at least partly caused by functional inactivation and thus offers a potential explanation for the significant hypofrontality of rCMRGlc observed in HD patients in this study and in that by Kuhl *et al.* (1982).

Since in previous studies no reduction of cortical rCMRGlc was found (Kuhl *et al.*, 1982), recent observations correlating rCMRGlc with clinical symptoms in HD patients (Young *et al.*, 1986; Berent *et al.*, 1988) have been performed exclusively for striatal rCMRGlc. As there is high interindividual variation of rCMRGlc in HD patients as well as in normal subjects, these authors have used indices of striatal metabolism normalized to maximal cortical rCMRGlc for this purpose. The use of these reference values, however, precludes the detection of possible relationships between cortical rCMRGlc and clinical symptoms. Since the cerebellar rCMRGlc seemed least affected in this group of HD patients, and since cerebellar rCMRGlc correlates significantly

with rCMRGlc in other brain regions in normal individuals, it seems appropriate to consider cerebellar rCMRGlc an 'internal standard' in patients with HD and to use cerebellar rCMRGlc as a reference value in this patient group. In addition to these normalized values this study reports on correlations between absolute values of rCMRGlc and the severity of symptoms in HD as well as between cortical ratios of striatal rCMRGlc and the clinical data. To our surprise, there was only a poor correlation between the degree of chorea as assessed by a clinical rating scale with both absolute rCMRGlc, the cortical ratio of rCMRGlc, and the cerebellar ratio (CR) of rCMRGlc in the striatum. This seems to be in contradiction to a study published by Young *et al.* (1986), demonstrating that rCMRGlc of the putamen normalized to the peak cortical activity correlated highly significantly with chorea in a group of 15 early to midstage HD patients. As the group of patients studied herein also included severely disabled patients, this discrepancy most likely is a result of differences concerning the severity of the disease in the two groups of patients studied. Chorea, which means hyperkinesia, is known to increase continuously to a peak in the midstage period of HD and to decrease from thereon as the patient sometimes even develops rigidity in later stages (Shoulson, 1981; Folstein *et al.*, 1986). Although neuroleptic treatment may suppress hyperkinesia (Adams and Victor, 1985) and thus might interfere with the validity of the correlation coefficients reported here between striatal metabolism and the degree of chorea, there was no major change of these correlation coefficients when the medicated patients were eliminated from the analysis (*see* Table 10). It therefore appears unlikely that in this group of patients the absence of a strong correlation between striatal metabolism and the degree of chorea is due to the inclusion of medicated patients.

Several authors have attributed the dementia of HD patients directly to pathology of the basal ganglia (McHugh and Folstein, 1975; Cummings and Benson, 1984). This concept was introduced approximately a decade ago (McHugh and Folstein, 1975) leading to the classification of the dementia encountered in HD patients as subcortical. The PET studies by Kuhl *et al.* (1982, 1984*a*) and Berent *et al.* (1988) reporting on normal cortical rCMRGlc in HD patients and on highly significant correlations between striatal rCMRGlc (normalized to cortical rCMRGlc) and psychometric test results in a group of early to midstage HD patients have lent considerable support to this concept. There are, however, only sparse clinical data to corroborate this concept (Whitehouse, 1986). In a CT study, Sax *et al.* (1983) found a positive and significant correlation between CT measures of caudate atrophy and cognitive function in a group of HD patients with both mild and severe impairment. In these patients cortical atrophy, however, was also present, and was reported to be worse in those patients with more severe impairment.

The data reported herein show that – in addition to a poor correlation of the degree of dementia with the CR for caudate rCMRGlc – the degree of dementia correlated best with the CR of mean cortical rCMRGlc in this group of HD patients. Even 2 correlation coefficients between absolute values of rCMRGlc in the frontoparietal and temporo-occipital cortex attained significance. In view of this observation the hypothesis that dementia in manifest HD is directly linked to subcortical pathology (Cummings and Benson, 1984) needs be reconsidered.

In the group of patients with HD studied here, the correlation coefficients between PET data and the severity of dementia were highest not in the frontal cortex, which seems the cortical region most severely affected in HD, but in the more posterior parts

of the brain (frontoparietal and temporo-occipital cortex). This may partly be due to the composition of the battery of psychometric tests used, since only the SKT includes frontal lobe oriented tasks. Nevertheless, the above-presented correlation coefficients between the PET data and the cognitive impairment of the HD patients show that the dementia encountered in this group of HD patients shares some common features with the dementia encountered in patients with Alzheimer's disease (AD). In AD patients, specific patterns of reduced rCMRGlc have been reported, with a reduction of rCMRGlc or $rCMRO_2$ in the parieto-occipital cortex prevailing also at an early stage of this disease (Frackowiak *et al.*, 1981; Foster *et al.*, 1983; de Leon *et al.*, 1983) and correlating with dementia (Chase *et al.*, 1987).

Many efforts have been made to assess the disability of HD in the performance of everyday tasks. The scale used in this study is a modification of the widely accepted Shoulson-Fahn scale and is supposed to measure the overall functional capacity of a patient with HD, thus encompassing deficits of many neuronal pathways. It is therefore not surprising to find that the CRs for most brain regions studied correlate significantly with the degree of disability.

Summarizing the above, it can be concluded that in patients with manifest HD, in addition to the more pronounced decrease of striatal rCMRGlc, a reduction of cortical rCMRGlc is also present, and that this reduction contributes to the severity of the clinical findings. As the reduction of cortical rCMRGlc correlated significantly with the degree of dementia, a modification of the concept of 'subcortical dementia' in HD patients seems to be indicated.

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REFERENCES

ADAMS RD, VICTOR M (1985) *Principles of Neurology*. Third Edition, New York: McGraw-Hill.

ALZHEIMER A (1911) Über die anatomische Grundlage der Huntingtonschen Chorea und der choreatischen Bewegungen überhaupt. *Neurologisches Zentralblatt*, **30**, 891–892.

ANTON G (1896) Über die Beteiligung der grossen basalen Gehirnganglien bei Bewegungsstörungen und insbesondere bei Chorea. *Jahrbücher für Psychiatrie und Neurologie*, **14**, 141–181.

BAXTER LR, MAZZIOTTA JC, PHELPS ME, SELIN CE, GUZE BH, FAIRBANKS L (1987) Cerebral glucose metabolic rates in normal human females versus normal males. *Psychiatry Research*, **21**, 237–245.

BENTON AL (1981) *Der Benton-Test*. Bern: Huber.

BERENT S, GIORDANI B, LEHTINEN S, MARKEL D, PENNEY JB, BUCHTEL HA, STAROSTA-RUBINSTEIN S, HICHWA R, YOUNG AB (1988) Positron emission tomographic scan investigations of Huntington's disease: cerebral metabolic correlates of cognitive function. *Annals of Neurology*, **23**, 541–546.

BRICKENKAMP K (1972) *Test d2–Aufmerksamkeits–Belastungstest*. Göttingen: Hogrefe.

BUDINGER TF, HUESMAN RH, KNITTEL B, FRIEDLAND RP, DERENZO SE (1985) Physiological modeling of dynamic measurements of metabolism using positron emission tomography. In: *The Metabolism of the Human Brain Studied with Positron Emission Tomography*. Edited by T. Greitz, D. H. Ingvar and L. Widén. New York: Raven Press, pp. 165–183.

CHAWLUK JB, ALAVI A, DANN R, HURTIG HI, BAIS S, KUSHNER MJ, ZIMMERMAN RA, REIVICH M (1987) Positron emission tomography in aging and dementia: effect of cerebral atrophy. *Journal of Nuclear Medicine*, **28**, 431–437.

CHASE TN, BURROWS GH, MOHR E (1987) Cortical glucose utilization patterns in primary degenerative dementias of the anterior and posterior type. *Archives of Gerontology and Geriatrics*, **6**, 289–297.

CUMMINGS JL, BENSON DF (1984) Subcortical dementia: review of an emerging concept. *Archives of Neurology, Chicago*, **41**, 874–879.

DAHL G (1972) *WIP Reduzierter Wechsler Intelligenz Test-Anwendung-Auswertung-Statistische Analysen-Normwerte*. Meisenheim-am-Glan: A. Hain.

DE LEON MJ, FERRIS SH, GEORGE AE, REISBERG B, CHRISTMAN DR, KRICHEFF II, WOLF AP (1983) Computed tomography and positron emission transaxial tomography evaluations of normal aging and Alzheimer's disease. *Journal of Cerebral Blood Flow and Metabolism*, **3**, 391–394.

DE LEON MJ, GEORGE AE, FERRIS SH, CHRISTMAN DR, FOWLER JS, GENTES CI, BRODIE J, REISBERG B, WOLF AP (1984) Positron emission tomography and computed tomography assessments of the aging human brain. *Journal of Computer Assisted Tomography*, **8**, 88–94.

DE LEON MJ, GEORGE AE, TOMANELLI J, CHRISTMAN D, KLUGER A, MILLER J, FERRIS SH, FOWLER J, BRODIE JD, VAN GELDER P, KLINGER A, WOLF AP (1987) Positron emission tomography studies of normal aging: a replication of PET III and 18-FDG using PET VI and 11-CDG. *Neurobiology of Aging*, **8**, 319–323.

DE VOLDER A, BOL A, MICHEL C, COGNEAU M, EVRARD P, LYON G, GOFFINET AM (1988) Brain glucose utilization in childhood Huntington's disease studied with positron emission tomography (PET). *Brain and Development*, **10**, 47–50.

DOM R, MALFROID M, BARO F (1976) Neuropathology of Huntington's chorea: studies of the ventrobasal complex of the thalamus. *Neurology, Minneapolis*, **26**, 64–68.

DUARA R, MARGOLIN RA, ROBERTSON-TCHABO EA, LONDON ED, SCHWARTZ M, RENFREW JW, KOZIARZ BJ, SUNDARAM M, GRADY C, MOORE AM, INGVAR DH, SOKOLOFF L, WEINGARTNER H, KESSLER RM, MANNING RG, CHANNING MA, CUTLER NR, RAPOPORT SI (1983) Cerebral glucose utilization, as measured with positron emission tomography in 21 resting healthy men between the ages of 21 and 83 years. *Brain*, **106**, 761–775.

EGGERS R, HAUG H, FISCHER D (1984) Preliminary report on macroscopic age changes in the human prosencephalon. A stereologic investigation. *Journal für Hirnforschung*, **25**, 129–139.

ERZIGKEIT H (1977) *Der Syndrom-Kurztest zur Erfassung von Aufmerksamkeits- und Gedächtnisstörungen*. Kless: Vaterstetten.

FOLSTEIN SE, LEIGH RJ, PARHAD IM, FOLSTEIN MF (1986) The diagnosis of Huntington's disease. *Neurology, Cleveland*, **36**, 1279–1283.

FOSTER NL, CHASE TN, FEDIO P, PATRONAS NJ, BROOKS RA, DI CHIRO G (1983) Alzheimer's disease: focal cortical changes shown by positron emission tomography. *Neurology, New York*, **33**, 961–965.

FRACKOWIAK RSJ, POZZILLI C, LEGG NJ, DU BOULAY GH, MARSHALL J, LENZI GL, JONES T (1981) Regional cerebral oxygen supply and utilization in dementia: a clinical and physiological study with oxygen-15 and positron tomography. *Brain*, **104**, 753–778.

GARNETT ES, FIRNAU G, NAHMIAS C, CARBOTTE R, BARTOLUCCI G (1984) Reduced striatal glucose consumption and prolonged reaction time are early features in Huntington's disease. *Journal of the Neurological Sciences*, **65**, 231–237.

GOFFINET AM, DE VOLDER AG, GILLIAN C, RECTEM D, BOL A, MICHEL C, COGNEAU M, LABAR D, LATERRE C (1989) Positron tomography demonstrates frontal lobe hypometabolism in progressive supranuclear palsy. *Annals of Neurology*, **25**, 131–139.

HAMACHER K, COENEN HH, STOCKLIN G (1986) Efficient stereospecific synthesis of no-carrier-added 2-[^{18}F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *Journal of Nuclear Medicine*, **27**, 235–238.

HATAZAWA J, BROOKS RA, DI CHIRO G, BACHARACH SL (1987*a*) Glucose utilization rate versus brain size in humans. *Neurology, Cleveland*, **37**, 583–588.

HATAZAWA J, BROOKS RA, DI CHIRO G, CAMPBELL G (1987*b*) Global cerebral glucose utilization is independent of brain size: a PET study. *Journal of Computer Assisted Tomography*, **11**, 571–576.

HAYDEN MR, HEWITT J, STOESSL AJ, CLARK C, AMMANN W, MARTIN WRW (1987) The combined use of positron emission tomography and DNA polymorphisms for preclinical detection of Huntington's disease. *Neurology, Cleveland,* **37,** 1441–1447.

HAYDEN MR, MARTIN WRW, STOESSL AJ, CLARK C, HOLLENBERG S, ADAM MJ, AMMANN W, HARROP R, ROGERS J, RUTH T, SAYRE C, PATE BD (1986) Positron emission tomography in the early diagnosis of Huntington's disease. *Neurology, Cleveland,* **36,** 888–894.

HERSCOVITCH P, AUCHUS AP, GADO M, CHI D, RAICHLE ME (1986) Correction of positron emission tomography data for cerebral atrophy. *Journal of Cerebral Blood Flow and Metabolism,* **6,** 120–124.

HOFFMAN EJ, HUANG SC, PHELPS ME (1979) Quantitation in positron emission computed tomography. I. Effect of object size. *Journal of Computer Assisted Tomography,* **3,** 299–308.

HOSOKAWA S, ICHIYA Y, KUWABARA Y, AYABE Z, MITSUO K, GOTO I, KATO M (1987) Positron emission tomography in cases of chorea with different underlying diseases. *Journal of Neurology, Neurosurgery and Psychiatry,* **50,** 1284–1287.

HUNTINGTON G (1872) On chorea. *Medical and Surgical Reporter,* **26,** 317–321.

KOEPPE R, FOSTER N, KUHL D (1989) Tissue atrophy alone cannot explain parietal hypometabolism in PET studies of Alzheimer's disease. *Journal of Nuclear Medicine,* **30,** Supplement, 895.

KRATZMEIER H, HORN R (1980) *Deutsche Bearbeitung zum Raven-Matritzentest.* Weinheim: Belz.

KUHL DE, PHELPS ME, MARKHAM CH, METTER EJ, RIEGE WH, WINTER J (1982) Cerebral metabolism and atrophy in Huntington's disease determined by ^{18}FDG and computed tomographic scan. *Annals of Neurology,* **12,** 425–434.

KUHL DE, METTER EJ, RIEGE WH, MARKHAM CH (1984*a*) Patterns of cerebral glucose utilization in Parkinson's disease and Huntington's disease. *Annals of Neurology,* **15,** S119–S125.

KUHL DE, METTER EJ, RIEGE WH, HAWKINS RA (1984*b*) The effect of normal aging on patterns of local cerebral glucose utilization. *Annals of Neurology,* **15,** S133–S137.

KUWERT T, LANGE HW, LANGEN K-J, HERZOG H, AULICH A, FEINENDEGEN LE (1989) Cerebral glucose consumption measured by PET in patients with and without psychiatric symptoms of Huntington's disease. *Psychiatry Research,* **29,** 361–362.

LANGE HW (1981) Quantitative changes of telencephalon, diencephalon, and mesencephalon in Huntington's chorea, postencephalitic, and idiopathic parkinsonism. *Verhandlungen der Anatomischen Gesellschaft,* **75,** 923–925.

LANGE H, THÖRNER G, HOPF A, SCHRÖDER KF (1976) Morphometric studies of the neuropathological changes in choreatic diseases. *Journal of the Neurological Sciences,* **28,** 401–425.

LANGE HW, STRAUSS W, HASSEL PC, WÖLLER W, TEGELER J (1983) Langzeittherapie bei Huntington-Kranken. *Psycho,* **5,** 286–290.

LANGE HW, AULICH A (1986) Die Hirnatrophie bei der Huntingtonschen Erkrankung. In: *Die Huntingtonsche Krankheit.* Edited by H. Oepen. Stuttgart: Hippokrates, pp. 25–40.

LANNOIS M, PAVIOT J (1897) Deux cas de chorée héréditaire avec autopsies. *Archives de Neurologie, Paris,* **4,** 333–334.

LAPLANE D, LEVASSEUR M, PILLON B, DUBOIS B, BAULAC M, MAZOYER B, TRAN DINH S, SETTE G, DANZE F, BARON JC (1989) Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions: neuropsychological, magnetic resonance imaging and positron tomography study. *Brain,* **112,** 699–725.

LEHRL S (1977) *Manual zum MWT-B.* Erlangen: Straube.

LEENDERS KL, FRACKOWIAK RSJ, QUINN N, MARSDEN CD (1986) Brain energy metabolism and dopaminergic function in Huntington's disease measured in vivo using positron emission tomography. *Movement Disorders,* **1,** 69–77.

MCCAUGHEY WTE (1961) The pathologic spectrum of Huntington's chorea. *Journal of Nervous and Mental Disease,* **133,** 91–103.

MCHUGH PR, FOLSTEIN MF (1975) Psychiatric syndromes of Huntington's chorea: a clinical and phenomenologic study. In: *Psychiatric Aspects of Neurological Disease.* Edited by D. F. Benson and D. Blumer. New York and London: Grune and Stratton, pp. 267–286.

MARTIN JB, GUSELLA JF (1986) Huntington's disease: pathogenesis and management. *New England Journal of Medicine,* **315,** 1267–1276.

MAZZIOTTA JC, PHELPS ME, PLUMMER D, KUHL DE (1981) Quantitation in positron emission computed tomography: 5. Physical-anatomical effects. *Journal of Computer Assisted Tomography,* **5,** 734–743.

MAZZIOTTA JC, PHELPS ME (1986) Positron emission tomography studies of the brain. In: *Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart*. Edited by M. E. Phelps, J. C. Mazziotta and H. R. Schelbert. New York: Raven Press, pp. 493–579.

MAZZIOTTA JC, PHELPS ME, PAHL JJ, HUANG S-C, BAXTER LR, RIEGE WH, HOFFMAN JM, KUHL DE, LANTO AB, WAPENSKI JA, MARKHAM CH (1987) Reduced cerebral glucose metabolism in asymptomatic subjects at risk for Huntington's disease. *New England Journal of Medicine*, **316**, 357–362.

MERZ J, LEHRL S, GALSTER V, ERZIGKEIT H (1975) MWT-B: Ein Intelligenzkurztest. *Psychiatrie, Neurologie und Medizinische Psychologie*, **27**, 424–428.

NIEUWENHUYS R, VOOGD J, HUIZJEN C VAN (1988) *The Human Central Nervous System: A Synopsis and Atlas*. Third revised edition. Berlin: Springer.

OEPEN G, OSTERTAG C (1981) Diagnostic value of CT in patients with Huntington's chorea and their offspring. *Journal of Neurology*, **225**, 189–196.

PENNEY JB, YOUNG AB (1988) Huntington's disease. In: *Parkinson's Disease and Movement Disorders*. Edited by J. Jankovic and E. Tolosa. Baltimore: Urban and Schwarzenberg, pp. 167–178.

PHELPS ME, HUANG SC, HOFFMAN EJ, SELIN C, SOKOLOFF L, KUHL DE (1979) Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Annals of Neurology*, **6**, 371–388.

RAVEN JC (1938) *Progressive Matrices*. London: H. K. Lewis.

REIVICH M, KUHL D, WOLF A, GREENBERG J, PHELPS M, IDO T, CASELLA V, FOWLER J, HOFFMAN E, ALAVI A, SOM P, SOKOLOFF L (1979) The [^{18}F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circulation Research*, **44**, 127–137.

REIVICH M, ALAVI A, WOLF A, FOWLER J, RUSSELL J, ARNETT C, MACGREGOR RR, SHIUE CY, ATKINS H, ANAND A, DANN R, GREENBERG JH (1985) Glucose metabolic rate kinetic model parameter determination in humans: the lumped constants and rate constants for [^{18}F]fluorodeoxyglucose and [^{11}C]deoxyglucose. *Journal of Cerebral Blood Flow and Metabolism*, **5**, 179–192.

RIEGE WH, METTER EJ, KUHL DE, PHELPS ME (1985) Brain glucose metabolism and memory functions: age decrease in factor scores. *Journal of Gerontology*, **40**, 459–467.

SAX DS, MENZER L (1977) Computerized tomography in Huntington disease. *Neurology, Minneapolis*, **27**, 388.

SAX DS, O'DONNELL B, BUTTERS N, MENZER L, MONTGOMERY K, KAYNE HL (1983) Computed tomographic, neurologic, and neuropsychological correlates of Huntington's disease. *International Journal of Neuroscience*, **18**, 21–36.

SHOULSON I (1981) Huntington disease: functional capacities in patients treated with neuroleptic and antidepressant drugs. *Neurology, New York*, **31**, 1333–1335.

SHOULSON I, FAHN S (1979) Huntington disease: clinical care and evaluation. *Neurology, New York*, **29**, 1–3.

SOKOLOFF L (1986) Cerebral circulation, energy metabolism, and protein synthesis: general characteristics and principles of measurement. In: *Positron Emisson Tomography and Autoradiography: Principles and Applications for the Brain and Heart*. Edited by M. E. Phelps, J. C. Mazziotta and H. R. Schelbert. New York: Raven Press, pp. 1–71.

SOKOLOFF L, REIVICH M, KENNEDY C, DES ROSIERS MH, PATLAK CS, PETTIGREW KD, SAKURADA O, SHINOHARA M (1977) The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *Journal of Neurochemistry*, **28**, 897–916.

STOBER T, WUSSOW W, SCHIMRIGK K (1984) Bicaudate diameter–the most specific and simple CT parameter in the diagnosis of Huntington's disease. *Neuroradiology*, **26**, 25–28.

SZIKLA G, BOUVIER G, HORI T, PETROV V (1977) *Atlas of Vascular Patterns and Cerebral Cortical Localization*. Berlin: Springer.

TALAIRACH J, TOURNOUX P (1988) *Co-Planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System: an Approach to Cerebral Imaging*. Stuttgart and New York: Georg Thieme.

TERRENCE CF, DELANEY JF, ALBERTS MC (1977) Computed tomography for Huntington's disease. *Neuroradiology*, **13**, 173–175.

TYLER JL, STROTHER SC, ZATORRE RJ, ALIVISATOS B, WORSLEY KJ, DIKSIC M, YAMAMOTO YL (1988) Stability of regional cerebral glucose metabolism in the normal brain measured by positron emission tomography. *Journal of Nuclear Medicine,* **29,** 631–642.

VONSATTEL J-P, MYERS RH, STEVENS TJ, FERRANTE RJ, BIRD ED, RICHARDSON EP (1985) Neuropathological classification of Huntington's disease. *Journal of Neuropathology and Experimental Neurology,* **44,** 559–577.

WHITEHOUSE PJ (1986) The concept of subcortical and cortical dementia: another look. *Annals of Neurology,* **19,** 1–6.

YOSHII F, BARKER WW, CHANG JY, LOEWENSTEIN D, APICELLA A, SMITH D, BOOTHE T, GINSBERG MD, PASCAL S, DUARA R (1988) Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy, and cerebrovascular risk factors. *Journal of Cerebral Blood Flow and Metabolism,* **8,** 654–661.

YOUNG AB, PENNEY JB, STAROSTA-RUBINSTEIN S, MARKEL DS, BERENT S, GIORDANI B, EHRENKAUFER R, JEWETT D, HICHWA R (1986) PET scan investigations of Huntington's disease: cerebral metabolic correlates of neurological features and functional decline. *Annals of Neurology,* **20,** 296–303.

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