Impaired Somatosensory Discrimination of Shape in Parkinson's Disease: Association With Caudate Nucleus Dopaminergic Function

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Abstract: Tactile discrimination of macrogeometric objects in a two-alternative forced-choice procedure represents a demanding task involving somatosensory pathways and higher cognitive processing. The objects for somatosensory discrimination, i.e., rectangular parallelepipeds differing only in oblongness, were presented in sequential pairs to normal volunteers and 12 parkinsonian patients. The performance of patients was significantly impaired compared to normal volunteers. From a biochemical point of view, the patients were characterized by a severely reduced 6-[¹⁸F]-fluoro-L-dopa (FDOPA) tracer metabolism in the basal ganglia, as measured using positron emission tomography (PET). Furthermore, reduced specific FDOPA metabolism in the putamen was consistent with the impaired motor capacities of the patients. The reduced specific FDOPA-uptake within the caudate nucleus was associated with additionally diminished somatosensory discrimination. This association, of low perception during task performance and decreased FDOPA-uptake, provides direct evidence for the role of the caudate nucleus in the cognitive part of the task. We suggest that directed attention and working memory were critically involved as a result of disturbed interactions between the head of the caudate nucleus and the dorsolateral prefrontal cortex. Furthermore, there were indications of an additional involvement of the mesolimbic system, which might be of importance during challenging situations such as forced choice. We conclude that differential effects on parts of the basal ganglia, during evolution of the degenerative process characteristic of Parkinson's disease, have profound consequences on the performance of skills, as shown here for a somatosensory discrimination task. *Hum. Brain Mapping 8:1–12, 1999.* © 1999 Wiley-Liss, Inc.

Key words: macrogeometric objects; somatosensory discrimination; Parkinson's disease; 6-[¹⁸F]-fluoro-L-dopa; dorsolateral prefrontal circuit; directed attention; working memory

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INTRODUCTION

Somatosensory discrimination of macrogeometric objects by tactile exploration in a two-alternative forced-choice procedure represents a demanding task which involves both sensorimotor pathways and higher cog-

nitive functions. The basic manual skill of tactile exploration is learned early during infancy [Ruff, 1984; Ledermann and Klatzky, 1987]. Simultaneous serial and sequential operations have to be executed. These include feature extraction from the objects explored and their digitized reconstruction in order to reach a final decision in on-line memory [Roland and Mortensen, 1987]. Using this task in patients with circumscribed lesions of the basal ganglia due to ischemic infarction, impaired information-processing and decision-making have been observed [Weder et al., 1994; Weder and Seitz, 1994]. Thus, this activation procedure may provide a model for studying the interaction between subcortical structures and distinct cortical areas in diseased states. In Parkinson's disease, deficits in a wide range of cognitive tests have been reported, including language ability, motor skills, memory, perceptual function, visuospatial function, problem-solving, and conceptual abilities [Pirozzolo et al., 1982]. Parkinsonian patients seem to register and store information correctly but may have a problem freely accessing that material [Weingartner et al., 1984]; frontal regulation of attention may be disturbed [Stam et al., 1993]. However, an important problem in most tests for the assessment of cognitive failures is the estimation of the role of reduced motor speed as causative cofactor [Loranger et al., 1972]. Nahmias et al. [1985] found reduced dopaminergic activity in the putamen but not in the caudate nucleus in the early motor manifestations of Parkinson's disease as assessed by 6- ^{18}F -fluoro-L-dopa (FDOPA) and positron emission tomography (PET), and assumed involvement of the caudate nucleus in associated cognitive deficits in later stages of the disease. In order to get insight into possibly disturbed information-processing during somatosensory discrimination, FDOPA has been measured in different parts of the basal ganglia, which are also relay nodes of segregated cortico-subcortical circuits [Alexander et al., 1986]. The aim of our study was to relate the performance of the above-described tactile discrimination task to FDOPA metabolism in the basal ganglia.

SUBJECTS AND METHODS

Subjects

The study population consisted of 12 parkinsonian patients, 8 males and 4 females, aged 41–66 years. Diagnostic criteria of parkinsonism were unequivocal [Quinn and Husain, 1986], and all individuals responded to levodopa therapy. The Mini Mental Status Scale revealed no evidence of significant mental deterioration [Folstein et al., 1975]. The patients were

assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) [Martínez-Martín et al., 1994]. Magnetic resonance (MR) imaging of the brain showed normal findings. Task performance of the patients was compared with the same in 12 normal volunteers (6 males and 6 females, aged 32–64 years). According to the Edinburgh Handedness Inventory, all subjects were right-handed [Oldfield, 1971].

Methods

The stimulation paradigm

The stimulation paradigm has been described by Roland and Mortensen [1987]. It has been applied in a PET activation study reported in preliminary form elsewhere [Weder et al., 1998a]. Seven pairs of polished aluminum parallelepipeds were used. These had identical volume, mass, and surface qualities, but differed in their oblongness. Differences of the major axes ranged from 0.44–5.01 mm, and the square bases varied between 0.17–1 mm. Subjects evaluated these objects by exploratory finger movements of the right hand only, and were not allowed to see them as their eyes were covered with cotton wool pads. The degree of difficulty varied, and discrimination was almost impossible for some pairs of parallelepipeds. The order of presentation of the cubes within a pair was random; the first cube was more oblong than the second as frequently as the reverse. The subjects were instructed to recognize as quickly as possible which of the two parallelepipeds was more oblong. If the individuals believed that the second object was more oblong, they were instructed to indicate this by raising the thumb of the exploring hand. In the other case, they were required to stop exploration to receive the first object of the next pair. An accidental loss of the order of cubes was signaled to the subject by the attending physician placing a fingertip on the exploring hand. A stimulation sequence under these forced-choice conditions lasted 4–5 min and was repeated three times. The exploratory finger movements and the answers of the subjects were recorded by videotape.

On the day of examination, the patients did not receive their early morning medication. The withdrawal of medication ranged from 14–18 hr, with an average of 15.7 hr.

FDOPA PET study

The FDOPA PET study was performed within 1 month after the stimulation task. Prior to examination, informed consent was obtained in accordance with

guidelines approved by the Ethics Committee of the Kantonsspital St. Gallen and the Declaration of Human Rights, Helsinki, 1975.

Since high amino-acid levels may influence FDOPA uptake [Leenders et al., 1985], the subjects of the study fasted before examination and, as in the stimulation session, levodopa therapy and dopaminergic agents were withheld overnight. One hour before tracer examination, a single oral dosis of 150 mg Carbidopa was given to inhibit peripheral decarboxylation. FDOPA was applied as an intravenous bolus of 4–5 mCi (150–190 MBq). Brain uptake was measured with PET for 2 hr. The seven-plane PET camera (ECAT 931–04/16 CTI, Siemens, Knoxville, TN) has a spatial resolution of 8 mm within and between planes. Head motion was restricted with an individually molded head restraint. Planes were aligned parallel to the orbito-meatal line, and the head was positioned such that the basal ganglia were in the center of the field of view of the camera.

Data analysis

Evaluation of the stimulation test

From the video recordings, the somatosensory discrimination rate and the percentage of correct discriminations were determined. Furthermore, dynamic explorative movements of the thumb, the most active finger during this task [Seitz et al., 1991], were analyzed on the videotapes, with a frame length of 45 msec. Additionally, the average time of contact with the object pairs was measured by means of random sample surveys.

For each pair of parallelepipeds, the percentage, or probability, of correct answers (PC) was given by each-subject estimates, i.e., the mean of the binomial distribution of responses, which were either correct (1) or incorrect (0). The dependence of PC (dichotomous outcome variable) on the difference of oblongness for a pair (continuous independent variable) was described by logistic regression [Dawson-Saunders and Trapp, 1990]. The single parameter describing dependence was computed using an iterative least-squares minimization program (EViews (QMS), Systat), running on a personal computer. If the program found no suitable parameter after 50 iterations, it exited.

Analysis of the FDOPA PET study

The data analysis was described by Antonini et al. [1995]. Using a standard template, regions of interest

(ROIs) were placed bilaterally on the putamen (250 mm²), head of the caudate nucleus (62.5 mm²), medial prefrontal cortex (440 mm²), and occipital cortex (515 mm²). From the image obtained between 60–120 min after bolus application, the radioactivity in the defined target regions (caudate nucleus, putamen, and medial prefrontal cortex) and reference regions (occipital cortex) was measured and normalized to the size of the region of interest (ROI), and the target:reference region ratio calculated [Leenders et al., 1990]. In addition, the FDOPA uptake rate constant (K_c) was calculated for each target ROI from the slope derived from a graphical analysis method [Patlak and Blasberg, 1985], using the occipital lobe ROI as brain reference. The K_c uptake rate constant was derived from the tissue slope-intercept plot between 30–90 min. The findings were compared to the reference data of our laboratory, consisting of 12 normal volunteers ranging in age from 50–60 years [Antonini et al., 1995].

Finally, the FDOPA PET studies were introduced into a computerized brain atlas program (CBA) [Greitz et al., 1990; Thurfjell et al., 1995]. After spatial standardization and normalization to the same global mean, average difference and variance images were calculated. Descriptive t-maps, testing the significance of the average differences for each voxel, were calculated in order to compare subgroups of the patients (see below, findings of FDOPA PET study). After thresholding, only ROIs consisting of more than 20 voxels were accepted in order to correct for limited spatial image resolution. Anatomical localization of ROIs was verified by overlay with the anatomical structures from the database of the CBA.

RESULTS

Patient data

The patient data are summarized in Table I. The mean duration of the disease was 7.7 years (range, 2–16 years). The total UPDRS score averaged 41.7 ± 14.3 (SD), compared to a maximum of 147. The average score can be decomposed into the following: mentation, behavior, and mood, 2.7 ± 1.7 (scale maximum, 16); activities of daily living, 15.5 ± 7.3 (scale maximum, 52); motor examination, 16.9 ± 5.9 (scale maximum, 56); and complications of therapy, 6.7 ± 5.4 (scale maximum, 23). Progression of disability over time in terms of increasing UPDRS score may be described for this group by the equation $y = 42.028 \cdot \text{LOG}(\text{years of disease duration}) + 6.998$ ($r = 0.73$). Apart from the parkinsonism, no other disturbance of the central or peripheral nervous system was present.

TABLE I. Patient data

Case	Age	Sex	Duration of disease (years)	Score according to UPDRS			Uptake rate constant (K _c) of FDOPA		Coefficient d for discrimination	
				Total	Part I ^a	Part III ^b	Putamen	Caudate nc.	Individuals	Groups
Subgroup A: Normal FDOPA uptake in caudate nucleus							0.00544 ^{c,d}	0.00905 ^c		0.45
1	66	F	4	35	2	10	0.00129	0.00831	0.38	
2	63	F	5	61	0	15	0.00684	0.01019	0.55	
3	41	M	2	20	0	14	0.00746	0.00915	0.44	
4	62	M	4	35	2	23	0.00607	0.00899	0.79	
5	56	M	8	38	5	21	0.00552	0.00861	0.41	
Subgroup B: Low FDOPA uptake in caudate nucleus							0.00366 ^{c,d}	0.00639 ^{c,d}		0.25
6	64	F	10	27	2	22	0.00285	0.00662	0.25	
7	65	M	13	60	2	20	0.00421	0.00644	0.37	
8	58	M	8	60	4	21	0.00337	0.00551	0.61	
9	53	M	8	50	3	5	0.00493	0.00776	0.0	
10	66	M	16	48	2	22	0.00264	0.00560	0.5	
11	56	F	10	21	5	9	0.00260	0.00588	0.07	
12	59	M	4	37	4	16	0.00499	0.00445	0.29	

^a Mentation, behavior, and mood.

^b Motor examination.

^c Mean value.

^d Significantly reduced ($< \bar{x} - 3 \text{ SD}$); for normal values, see text.

Task performance

Motor performance

The mode of exploration of the objects corresponded to the description by Roland and Mortensen [1987], and Seitz et al. [1991]. Generally, the exploratory movements of the patients were slowed. The frequency of the thumb, the most important exploring finger in this sort of task, was 2.1 per sec in the normal volunteers and 1.4 per sec in the patients. This difference is highly significant ($P < 0.001$), as determined by two-tailed t-test. The exposition time of the objects to the exploring hand was in the same range for both groups. On average, a pair of objects was explored for 7.6 sec (first object, 4.1 sec; second object, 3.5 sec) in the normal volunteers, and for 8.4 sec (first object, 4.8 sec; second object, 3.6 sec) in the patients. In 5 patients a slight to moderate tremor of the legs and the contralateral hand occurred. In one patient the exploring movements had a slightly dyskinetic appearance, and in another patient associated movements contralateral to the exploring hand were observed.

Information processing

The normal volunteers discriminated 6.7 ± 1.74 (mean $\pm$ SD) pairs of parallelepipeds/min and made

on average $72 \pm 5.85\%$ (mean and SD) correct discriminations. The corresponding values for the parkinsonian patients were 5.6 ± 1.85 pairs of parallelepipeds/min and $65 \pm 7.96\%$ correct discriminations. The percentage of correct answers was significantly different in the two groups ($P = 0.02$, two-tailed t-test). The discrimination rates of the two groups were comparable ($P = 0.24$).

The binomial distribution of right and wrong answers showed gradually better discriminations with increasing differences of the major axes in a pair. The dependence of the probability of correct discriminations on differences of major axis (Fig.1a) could be described by the formula for logistic regression given in Equation 1 (see footnote¹). Note that: 1) logistic regression curves, describing task performance, can be computed both for groups and individuals; 2) the logistic regression curve is invertible, permitting a critical axis difference to be calculated from the threshold for conscious perception, which is assumed to be $PC = 0.75$ [Roland and Mortensen, 1987]; 3) the critical axis difference ($\Delta l \approx 2 \text{ mm}$) implies that differences of the major axes, varying between 0.44–5.01 mm, were responsible for recognition of the differences in oblongness, since differences of the minor axes of the square

¹ $PC = 1 / (1 + e^{-d \cdot \Delta l})$ (equation 1)

Figure 1.

a: Task performance of a subject as described by logistic regression. The curve was obtained by iterative computation (see text) and corresponds to the equation 1. It depends on the side-length difference of the major axis as independent variable and the coefficient d . The latter describes the efficiency of the individual tested. The example shown describes a rather efficient individual ($d = 0.61$) with a total of 72% correct discriminations. The calculated curve is a fit to the seven observed discriminations represented by the squares. **b:** Logistic regression curves of normal volunteers (circles) and patients with normal (squares) and reduced (triangles) FDOPA metabolism in the caudate nucleus are displayed. Definite impairment is evident in the patients, especially for those with reduced FDOPA metabolism.

bases were less than the critical axis difference [Weder et al., 1998a]; 4) the regression curve describing this analysis originates exactly at $\Delta l = 0$ for equal side lengths and $PC = 0.5$, indicating chance responses, and approaches asymptotically the value of 1, implying certain correct responses; and 5) the coefficient d in Equation 1 is an indicator for the degree of perceived somatosensory discrimination.

Figure 2.

The scattergram demonstrates the relation between the coefficient d for somatosensory discrimination and the average exploration time of a pair of objects. Among the patients (open symbols), individuals with normal (rectangles) and reduced (triangles) FDOPA metabolism in the caudate nucleus are distinguished. By comparison, normal volunteers were more efficient (solid circles).

The coefficient d was significantly reduced ($P = 0.003$ using a two-tailed t -test) in the parkinsonians, ranging from 0–0.79 with a mean of 0.35, compared to its value for normal volunteers, for whom it ranged from 0.47–1.06 with a mean of 0.65 (Table I). In addition, the coefficient d gave a differentiated measure of performance of the task. It unmasked individuals who guessed rather than recognized the side length differences. That occurred when an individual did not reach the critical threshold in the vicinity of $PC = 0.75$, as indicated by a low coefficient d .

No single clinical, behavioral assessment factor correlated with performance deficits. No definite influence upon the results could be recognized either in cases of interfering tremor, dyskinesia, and associated movements, or in cases with severe motor involvement. The subjects showed equal task performance over the mean exploration time per pair observed (Fig. 2). Prolonged exploration time was not consistently associated with a better score. Five patients lost the right order temporarily during the task, as indicated by an answer after the first object was presented, a mistake not observed in normal volunteers.

No age effects were found: t -tests were performed for all pairs of parallelepipeds, whether regression coefficients for a linear relationship between correct discriminations and age were different from zero or

Figure 3.

Box plot of FDOPA metabolism within caudate nucleus (NC CAUD), putamen, and medial frontal cortex (FT CORTEX) in normal volunteers (n) and parkinsonian patients (p). The values represent the ratios of uptake between the target regions and the occipital cortex as reference region. The uptake in the basal ganglia of patients is significantly decreased, predominantly in the putamen.

not. The hypothesis of a horizontal regression relating correct discriminations for all pairs of parallelepipeds and age could not be rejected, since the observed *t*-statistics were within the 95% confidence interval.

Findings of FDOPA PET study

In patients, the target ROI:reference ROI ratio showed a considerably reduced FDOPA uptake in the nuclei of the basal ganglia, whereas the metabolism within the prefrontal cortex was only insignificantly reduced (Fig. 3). FDOPA-uptake declined regularly with disease duration within the putamen (target ROI:occipital ROI ratio, $y = -0.993 \cdot \text{LOG}(\text{disease duration in years, } x) + 2.44$; $r = 0.89$). In contrast, the decline in the caudate nucleus was less systematic ($y = -0.648 \cdot \text{LOG}(x) + 2.496$; $r = 0.56$). Thus, FDOPA metabolism within the putamen was more severely affected (average uptake reduction by 30.8% from the normal mean) than within the caudate nucleus (18.6%). When evaluating both sides separately, an insignificantly accentuated diminution within the nuclei of the left basal ganglia was present.

In patients, average constant *K_c* in the putamen was 0.00437 ± 0.00188 (mean $\pm$ SD) and in the caudate nucleus 0.00729 ± 0.00178 , compared to $0.00967 \pm$

0.00078 and 0.01136 ± 0.00115 , respectively, in normal volunteers. This constant was linearly correlated with the striato-occipital radioactivity ratio (correlation coefficient $r = 0.92$ for the putamen, and $r = 0.84$ for the caudate nucleus). In contrast to the values in the putamen, *K_c* values in the caudate nucleus of 5 patients were normal (average *K_c* $\pm$ 3 SD) (Table I). Dividing the patients into two subgroups, i.e., group A ($n = 5$) with normal FDOPA-uptake in the caudate nucleus and group B ($n = 7$) with reduced uptake, revealed in a percentile comparison (Fig. 4a) that group A performed the discrimination task better than group B. Direct comparison of the coefficient *d* with an unpaired *t*-test revealed a trend difference between the two subgroups ($P = 0.095$). A striking difference was demonstrated only in the comparison of normal volunteers with group B, which yielded $t = 3.92$ ($P = 0.001$). On the other hand, the comparison of group A with normal volunteers yielded $t = 1.6$ ($P = 0.14$).

In the group analyses, coefficients *d* of 0.45 and 0.25, respectively, were found in subgroups A and B (Fig. 1b). Logarithmic transformation of Equation 1 permits the coefficient *d* to be described by a linear relation between differences in length of the cubes and the logarithm of the probability of a wrong answer (see footnote²). Pairwise comparison of this relation in the different groups led to the rejection of the hypothesis of equal slopes, i.e., coefficients *d*. The corresponding *F*/*P*-values were 19.05/0.000 for normal volunteers vs. subgroup A, 51.37/0.000 for normal volunteers vs. subgroup B, and 7.85/0.012 for subgroup A vs. subgroup B. Here, *F*/*P* indicates the probability *P* that the *F*-distributed test criterion exceeds the value *F*. In contrast to the better task performance according to coefficient *d*, loss of the right order occurred more frequently in the individuals of subgroup A (score of 2.28 by using *z*-approximation in order to compare the proportions, $P < 0.05$, two-tailed).

Additionally, we compared the probability of a right answer, PC, in the subgroups by calculation of the odds ratio, including the 95% confidence interval [Dawson-Saunders and Trapp, 1990], below and above the supposed critical threshold for conscious perception (Fig. 4b) [Weder et al., 1988a]. At a difference of the major axis of 1.02 mm within a pair, no definite change of the relationship between right and wrong answers could be ascertained between the different subgroups. However, at a difference of 3.97 mm, the odds ratio indicated better perception in the normal volunteers

² $d = -(1/\Delta l) \cdot \ln(1 - PC/PC)$ (equation 2)

Figure 4.

a: Percentiles comparison for somatosensory discrimination in patients according to normal (n, subgroup A) and low uptake (l, subgroup B) of FDOPA in the caudate nucleus. Displayed are the points corresponding to the 10th, 25th, 30th, 40th, 50th, 60th, 75th, and 90th percentiles of coefficient d, permitting the determination of the coefficient in either group. The coefficient of subgroup B lies uniformly below the line of identity, indicating a worse performance of the task when there is significant involvement of the caudate nucleus. b: Estimate of the probability of a

right answer, PC, in subgroup A vs. subgroup B as expressed by the odds ratio, including the 95% confidence interval. Here, the observations on pairs below and above threshold-level of normal volunteers [see Weder et al., 1998a], i.e., discriminations of parallelepipeds with a difference of the major axis, Δl , of 1.02 and 3.97 mm were illustrated. Since the confidence interval does not include the value of 1, we may be 95% confident that subgroup B is characterized by a better task performance above the critical threshold.

(vs. subgroup A, 3.9; 1.71–8.76 [mean, 95% confidence interval]; vs. subgroup B, 8.61; 4.14–17.81) and in subgroup A (vs. subgroup B, 2.21; 1.09–4.48) [Dawson-Saunders and Trapp, 1990].

Comparing motor deficits according to UPDRS (part III), the score of the motor examination was in the same range for subgroups A and B, with a mean difference of 3.6 ($P = 0.33$, two-tailed t-test). The movement frequency of the thumb was slower in subgroup A by a mean of 0.3 per sec ($P = 0.034$). The total exploration time of a pair of objects was similar in both groups, with a minimal mean difference of 0.42 sec ($P = 0.86$). No significant difference between the two subgroups could be recognized in mentation, behavior, and mood according to UPDRS (part I), which yielded a mean difference of 1.68 ($P = 0.08$).

Descriptive t-maps, testing for a difference between independent means, showed a greater breakdown of FDOPA metabolism in several structures in subgroup B compared to subgroup A ($t > 2.23$, $P < 0.05$). These areas were related to several subcortical structures and the mesial frontal cortex on both sides: the head of the caudate nucleus and globus pallidus on the left side, the medial and dorsal part of the thalamus on the right side, and the nucleus subthalamicus and the anterior cingulate cortex on both sides (Fig. 5).

DISCUSSION

We have described a group of patients with Parkinson's disease who showed failure in somatosensory discrimination of pairs of parallelepipeds differing only in oblongness. The parkinsonians were characterized by a severely reduced FDOPA metabolism within the putamen and, accordingly, by slowed finger movements. Task performance was impaired in patients in comparison to normal volunteers, as evident from the descriptive statistics of discrimination results. The degree of motor restraints was similar among the patients, and was associated with impaired, probably low-level information processing, i.e., reduced feature extraction during tactile exploration. However, a subgroup could be distinguished, with involvement of the head of the caudate nucleus in the underlying degenerative process. Most of the individuals constituting this subgroup did not perceive explicitly the intended information. Behavioral features of these individuals may have included a loss of capacity in working memory, since episodic memory proved to be very susceptible to distractors [Goldman-Rakic, 1989]. This observation provided direct evidence that dopaminergic deficiency within the caudate nucleus interfered with cognitive processes operative during the task.

Figure 5.

Descriptive t-maps in standardized CBA space [Greitz et al., 1990; Thurfjell et al., 1995], representing the hypothesis that the independent means of the two subgroups A and B (see text) with respect to FDOPA-uptake differ with a search threshold of $t > 2.33$ ($P < 0.05$). To correct for image resolution, a minimal cluster size of 20 voxels was also required of regions of interest (ROIs). Slices are shown as viewed from below, so that the right hemisphere appears on the left. In order to delineate the ROIs, the

caudate nucleus, globus pallidus, putamen, nucleus subthalamicus, and cingulate cortex from the data bank of the CBA were displayed. Reduced FDOPA-uptake in subgroup B was found predominantly at relay nodes of "dorsolateral-prefrontal" and "anterior cingulate" circuits:¹¹ head of the caudate nucleus (B,C) and globus pallidus (A) on the left side, ventral and anterior thalamus (B,C) on the right side, and anterior cingulate cortex on both sides (A,B).

Furthermore, breakdown of FDOPA metabolism in the caudate nucleus may be of significance for subcortical-cortical interactions, especially with the dorsolateral prefrontal cortex, which mediates functions such as directed attention and working memory [Alexander et al., 1986; Fletcher et al., 1997].

Two-alternative forced-choice discrimination of objects includes a sequence of operations, i.e., feature extraction during tactile exploration, reconstruction of an internalized representation of the two objects felt, comparison in on-line memory, and final decision-making [Roland, 1993]. Each of these steps is potentially vulnerable to the disease process. From a neuropathological point of view, degeneration of dopamine-containing neurons raises the question of subcortical-cortical disruption produced by the disease process and the site of interaction with the aforementioned operations. The dopaminergic system is organized into ascending nigrostriatal, mesocortico-limbic, and hypothalamic pathways, and a descending system to the spinal cord [Agid et al., 1987; Scatton et al., 1983]. In PET studies using FDOPA, Nahmias et al. [1985] and Leenders et al. [1990] showed a regular and definitely impaired tracer-uptake in the putamen correlated with the severity of motor symptoms. In contrast, FDOPA-uptake in the caudate nucleus remained normal or was slightly decreased in the early stages, whereas severe

reduction was observed only in the late stage. This substantiated the postmortem findings of Hornykiewicz [1981], who found a more severe dopamine depletion in the putamen than in the caudate nucleus in patients with Parkinson's disease. Considering the duration of the disease, individuals with low FDOPA-uptake in the caudate were in a more advanced stage of the disease.

The putamen is thought to be an integral part of a motor circuit which interconnects the motor and premotor cortex with the substantia nigra and globus pallidus, and the ventral lateral nuclei of the thalamus, respectively [Alexander et al., 1986]. The importance of the putamen for implicit motor learning and final motor skill acquisition was demonstrated by Hazeltine et al. [1997] and Seitz and Roland [1992] in studying sequential finger movements with PET. In accordance with that data, the dopaminergic deficit within the putamen was reflected by significantly reduced finger movements in our patients. In Parkinson's disease, the resulting motor effect typically concerns sequential and complex movements [Benecke et al., 1987], exemplified in our study by the manual skill of tactile exploration. Others have found that motor degradation does not preclude somatosensory discrimination by tactile exploration [Freund, 1987; Roland, 1987]. However, feature extraction per time and, thus, infor-

mation flow and processing may have been significantly reduced in the Parkinson patients, since tactile exploration was slowed. We suggest that diminution of active touch, the basis of tactile exploration [Gibson, 1962; Wall, 1970], interfered with task performance in all patients at elementary or low-level information processing, respectively, of information sampling. As the two subgroups of patients showed similar motor restraints with a pronounced slowness of finger movements in the more successful individuals, severely reduced perception of patients with low FDOPA-uptake in the caudate cannot be explained by impaired exploration. Accordingly, reduced efficiency in somatosensory discrimination, expressed by the coefficient d , did not correlate with thumb frequency either in normal volunteers or in the parkinsonians. Also, some patients were successful in performing the task at the range of normal volunteers despite motor disability and without extra time for exploration.

The parameter obtained by logistic regression, i.e., coefficient d , allowed a perfect discrimination between groups and subgroups; one subgroup of patients, as defined by reduced FDOPA-uptake in the head of the caudate nucleus, was distinguished by poor performance of the task. As reported in detail recently, the coefficient d provides an estimate of conscious perception [Weder et al., 1998a]. Related to somatosensory discrimination, guidance of behavior by working memory is essential for successful information processing [Goldman-Rakic, 1989]: the subjects have to select pertinent information and hold that information "on-line" during the temporal interval for which a decision, i.e., discrimination of the two objects, has to be performed. During performance of the task, the subjects have to concentrate both on object differences and on the order of the cubes, i.e., their attention was divided [Corbetta et al., 1990]. The difficulty of retaining multiple information in episodic memory became evident in both patient subgroups. However, patients with normal FDOPA-uptake in the caudate coped better with the task in that they acquired the specific somatosensory information more effectively. In contrast, patients with low FDOPA-uptake in the caudate were significantly distracted by aspects of the procedural plan of the task, i.e., the order of the cubes. Hence, these patients were preferentially susceptible to distractors, which is characteristic of a loss in capacity of working memory [Goldmann-Rakic, 1989]. This observation underlines the selective character of attention which provides final perception of sensory information. Obviously, conceptual abilities failed in subgroup B to get the relevant and to dismiss efficiently the irrelevant information. Most of these subjects did

not perceive the intended information explicitly. Relying on these behavioral aspects, we suggest a second failure of high-level information processing, confined mainly to subjects with low FDOPA-uptake in the caudate (see Fig. 4b).

In monkeys, ablation of the anterodorsal sector of the head of the caudate nucleus resulted in a severe impairment of a spatial memory task, i.e., the so-called "spatial delayed alternation task" [Divac et al., 1967]. Similarly, animals were disturbed in performing spatial delayed response and spatial delayed alternation after destruction of the mediodorsal nucleus of the thalamus [Isseroff et al., 1982]. These results were interpreted as a specific syndrome of spatial memory loss and corresponded to memory impairments characteristic of prefrontal cortex damage in monkeys [Goldman et al., 1971]. The data suggested that the dorsolateral prefrontal cortex and its subcortical projection areas in the caudate nucleus and in the mediodorsal and other thalamic nuclei form a system which mediates aspects of spatial memory. Further evidence for the importance of such a system for mnemonic processes was derived from single-cell recording studies [Fuster and Alexander, 1973; Fuster, 1981; Goldman et al., 1971]. Relying on this anatomical and physiological evidence, a concept of segregated cortico-subcortical circuits was formulated [Alexander et al., 1986]. Sawaguchi et al. [1990a] reported that dopamine augmented activity of prefrontal neurons in monkeys, related to delayed response task. The reverse effect was observed after application of dopamine antagonists [Sawaguchi et al., 1990b]. Similarities between delayed-response tasks in the animals and the Wisconsin card sort test, used for the assessment of frontal lobe dysfunction in humans, are derived from the assumption that the correct response must be provided from representational memory [Goldman-Rakic, 1989]. This has to be supposed also for our task, since internalized representation of the objects is a prerequisite for the comparison of the consecutively explored parallelepipeds in on-line memory. In this context, our interest concentrated on the dorsolateral prefrontal circuit [Alexander et al., 1986]. This circuit is suggested to have relays at the dorsolateral prefrontal cortex, at the head of the dorsolateral caudate nucleus, at the medial-dorsomedial globus pallidus and rostromedial substantia nigra, and at the ventral-anterior and medial-dorsal part of the thalamus. In the categorical comparison of both subgroups, one aspect is that traces of the aforementioned loop are recognizable, as indicated by the additional deficits in the subgroup with low FDOPA-uptake in the caudate nucleus. However, the significance of our observation for the medio-

dorsal thalamus has to be validated in further studies in humans, since connectional studies in animals have shown that the thalamus is largely bypassed by dopamine axons [Steriade and McCarley, 1990].

In humans, Caplan et al. [1990] found in a retrospective analysis of ischemic caudate infarction cognitive and behavioral abnormalities such as spatial hemineglect (3 out of 11 cases) and abulia (4/11). On the other hand, activation of the dorsolateral prefrontal cortex, especially the right Brodmann areas 9, 10, and 46, has been shown during episodic retrieval in activation procedures [Fletcher et al., 1997]. Lateralization seems to depend on the inherent requirements of a task, i.e., retrieval of information from episodic memory (right hemisphere) vs. encoding memory (left hemisphere). As has been shown in normal volunteers, somatosensory discrimination involves the dorsolateral prefrontal cortex on the right hemisphere [Seitz et al., 1991]. In Parkinson's disease, impaired activation of the dorsolateral prefrontal cortex was found by Playford et al. [1992] in a positron emission tomography study of an internally cued motor task. Our preliminary data point to an activation deficit during somatosensory discrimination within the right dorsolateral prefrontal cortex in Parkinson patients [Weder et al., 1998b]. Recently, Doyon et al. [1998] found direct evidence for disruption of the normal pattern of basal ganglia outflow onto the prefrontal cortex in Parkinson patients performing a well-learned sequence of movements. Both the behavioral anomalies observed in our patients and the associated decreased FDOPA-metabolism in the basal ganglia correspond well to the model of interference between subcortical structures and distinct cortical areas. Again, subjects of subgroup B in particular, with low FDOPA-uptake in the caudate, failed in perception. The poorest task performances were at the level of pure guessing. Obviously, these patients failed to adopt a successful retrieval mode for the intended information. Conceptual abilities have been described in activities involving the prefrontal cortex [Owen et al., 1996] and thus seem to depend on dopaminergic modulation.

In the categorical comparison of both subgroups with respect to FDOPA-uptake in the caudate nucleus, the affection of the medial part of subthalamic nucleus and the anterior cingulate cortex may indicate that limbic pathway is of significance for our task [Agid et al., 1987; Parent and Hazrati, 1995]. In Parkinson's disease, evidence for degeneration of dopaminergic neurons in mesocorticolimbic structures has been found [Scatton et al., 1983]. A motivational component of attention has been attributed to the limbic system and, therefore, degradation may devalue sensation in the

affected hemispace [Mesulam, 1990]. Paus et al. [1993] supposed a modulatory effect of the anterior cingulate cortex to be of importance in new and challenging situations. In oculomotor and manual tasks, this area was only involved during concomitant activation of prefrontal cortex. Pardo et al. [1991] segregated aspects of attention by performing a pure vigilance task. Under these conditions, activation was restricted to an attentional system consisting of the right dorsolateral prefrontal cortex and parietal cortex (Brodmann area 7), whereas the anterior cingulate cortex remained inactive. Berns et al. [1997] extended this idea in that they distinguished between maintenance of contextual information within the dorsolateral prefrontal cortex, and the mental effort to recognize novel information, which is monitored by the ventral striatum and the connected anterior cingulate cortex. Dopaminergic modulation of impaired cognitive activation in the anterior cingulate could be demonstrated by Dolan et al. [1995] through the application of apomorphin in schizophrenic patients. Novelty and retrieval efforts were features operative during our task, since consecutive pairs of parallelepipeds varied in difference, and somatosensory discrimination was performed under forced-choice conditions.

CONCLUSIONS

The important finding from this study is that somatosensory discrimination deficits correlate strongly with direct evidence of diminished dopamine uptake in the head of the caudate nucleus, and that these deficits are not related to the manual clumsiness normally characteristic of Parkinson's patients. The implications of this finding require further study, especially in relation to the normal behavior of the prefrontal and mesial frontal cortex in patients doing cognitive tasks with and without motor components. The cerebral activation pattern, observed in the same study group, substantiated the assumption that breakdown of dopaminergic activity at the head of the caudate nucleus disturbs the functional integrity of the prefrontal cortex [Weder et al., 1998b].

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