

# Globus pallidus dopamine and Parkinson motor subtypes

## Clinical and brain biochemical correlation



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### ABSTRACT

**Background:** Patients with Parkinson disease (PD) may be akinetic/rigid, be tremor dominant, or have comparable severity of these motor symptoms (classic). The pathophysiologic basis of different PD phenotypes is unknown. This study assessed pallidal and striatal dopamine level patterns in different motor subgroups of PD and normal control brains.

**Methods:** Globus pallidus and striatum dopamine (DA) levels were measured with high performance liquid chromatography in eight autopsy confirmed PD and five control frozen brains.

**Results:** DA levels in the external globus pallidus (GPe) of normal brains were nearly six times greater than in the internal pallidum (GPi). In PD, the mean loss of DA was marked (−82%) in GPe and moderate (−51%) in GPi. DA loss of variable degree was seen in different subdivisions of GPe and GPi in PD; however, DA levels were near normal in the ventral (rostral and caudal) GPi of PD cases with prominent tremor. There was marked loss of DA (−89%) in the caudate and severe loss (−98.4%) in the putamen in PD. The pattern of pallidal DA loss did not match the putaminal DA loss.

**Conclusion:** There is sufficient loss of dopamine (DA) in external globus pallidus and the internal globus pallidum (GPi) as may contribute to the motor manifestations of Parkinson disease (PD). The possible functional disequilibrium between GABAergic and DAergic influences in favor of DA in the caudoventral parts of the GPi may contribute to resting tremor in tremor dominant and classic PD cases. *Neurology*® 2008;70:1403-1410

### GLOSSARY

**CN** = caudate nucleus; **DA** = dopamine; **GPe** = external globus pallidus; **GPi** = internal globus pallidum; **LB** = Lewy body; **MDCS** = Movement Disorder Clinic in Saskatoon; **PD** = Parkinson disease; **PUT** = putamen; **VTA** = ventral tegmental area.

Rigidity, akinesia/hypokinesia/bradykinesia (bradykinesia), and resting tremor are main motor features of idiopathic Parkinson disease (PD). Some cases are tremor dominant, some are akinetic/rigid, while the severity of these symptoms is comparable in others.<sup>1-3</sup> Studies of brains from such patients are necessary to understand pathophysiology of PD phenotypes as no suitable animal models are available.

Marked substantia nigra compacta dopamine (DA) neuronal loss, intraneuronal Lewy body (LB) inclusions,<sup>4</sup> and severe DA deficiency in caudate, putamen, globus pallidus (GP), nucleus accumbens, and subthalamic nucleus are characteristic of PD.<sup>5</sup> Late in the course, there are likely additional, non-DAergic changes in the brain.

Loss of nigral modulatory influence on the basal ganglia disrupts the normal function within cortical-basal ganglia-thalamic-cortical circuits.<sup>6,7</sup> Putamen receives input from the motor and premotor cortical areas and projects directly and indirectly onto the internal globus pallidus (GPi)/substantia nigra reticulata.<sup>6,7</sup>

The role of nigrostriatal DA in the pathophysiology of PD is well known,<sup>5,8-10</sup> but there is limited information on DA's role in the two pallidal complexes in normal and

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PD brains. The pallidal segments are innervated by nigral or ventral tegmental (VTA) DA fibers, by separate fiber system and by collaterals of nigrostriatal fibers.<sup>11-13</sup> Thus pallidal DA may modulate the motor circuit.

The aim of our study was to establish regional and subregional DA patterns in the GPe and GPi in normal and in PD brains, and to compare those in different motor subtypes of PD. We analyzed eight autopsied brains of patients with PD and five neurologically normal controls.

**METHODS** All patients were assessed at the Movement Disorder Clinic in Saskatoon (MDCS). As a rule, they were followed at 6- to 12-month intervals.<sup>14,15</sup> Hoehn and Yahr stage<sup>16</sup> and severity of bradykinesia, rigidity, and tremor were assessed at every clinic visit. Prior to 1987, the severity of bradykinesia, rigidity, and tremor were measured by Webster scale.<sup>17</sup> For this report, the Webster scale values were converted to the equivalent values on the UPDRS scale.<sup>18</sup> Levodopa-related response fluctuations and dyskinesia were evaluated at each MDCS visit and reported as cumulative incidence.<sup>15</sup>

Autopsy was performed within 24 hours of death after a written consent from the next of kin. Five control brains were obtained from individuals who had no neurologic disease and no evidence of brain pathology. Immediately after autopsy, one-half of the brain was fixed in formalin for neuropathologic examination<sup>14,15</sup> and the other half frozen at  $-80^{\circ}\text{C}$  for biochemical studies. Only those cases that had pathologically confirmed LB disease and no concurrent pathology (which may modify parkinsonian features) were included in this study. The autopsies were performed between 1990 and 1996.

We identified eight patients who manifested a consistent pattern of tremor, bradykinesia, and rigidity throughout the follow-up. Based on the combination of these symptoms, patients were divided into three subgroups. Group I were patients ( $n = 3$ ) who had prominent bradykinesia and rigidity, but no visible tremor, and were classified as akinetic/rigid

cases. Group II consisted of three patients who had comparable severity of bradykinesia, rigidity, and tremor, and were classified as classic cases. Group III were two patients in whom the tremor was the dominant feature compared to bradykinesia and rigidity—the tremor dominant cases.

The frozen half brains were thawed to approximately  $-10^{\circ}\text{C}$  and cut by hand in the frontal plane in 2 to 3 mm thick slices, starting at the anterior border of the caudate head. For the caudate nucleus (head), samples from slices 2 to 5 were used and for the putamen from slices 5 to 11. For the GPe and GPi, four slices were used, two rostral and two caudal, taken between the crossing of the anterior commissure and the anterior border of the subthalamic nucleus (slices no. 7 to 10, as a rule). (The most rostral and the most caudal poles of the GPe were not included in this study.) Each of the isolated rostral and caudal pallidal subdivisions was further subdivided into a dorsal and a ventral portion. This procedure permitted a detailed rostrocaudal and dorsoventral DA distribution study in both pallidal segments. Care was taken to exclude from the pallidal samples the lateral and medial pallidal medullary laminae, so as to avoid contamination with the densely packed nigrostriatal DA fibers coursing through these structures to reach the striatum (putamen). The dissected tissue samples were stored at  $-80^{\circ}\text{C}$  until analysis, performed within 6 weeks of dissection.

Biochemical analyses of the tissue from the caudate, the putamen, and the GP were performed using high performance liquid chromatography with electrochemical detection, as described by Felice et al.<sup>19</sup> and modifications as described previously.<sup>20,21</sup> The analyses were performed blinded to the clinical information on the patients. DA concentrations were expressed as nanograms (ng) per gram (g) of fresh tissue. Student two-tailed *t* test and, where applicable, the paired *t* test were used to identify statistical significance. A *p* value of  $<0.05$  was considered significant.

**RESULTS** Eight PD cases (five men and three women) were included in the study. Table 1 is a summary of the major clinical features in these patients. Group I (akinetic/rigid) included one woman and two men, Group II (classic) included one woman and two men, and Group III (tremor dominant) consisted of one woman and one man. The mean age at PD onset in the eight patients was 62.1 years (50 to 80 years) and the mean age at death was 80.6 years (74 to 89 years). The mean duration of follow-up at the MDCS was 13 years (4.9 to 24.6 years) and the mean duration of illness until death was 18.5 years (9 to 33 years). All patients received levodopa for a mean 13.8 (6.5 to 24.3) years. Dyskinesias were observed in four patients, two in Group I, one in Group II, and one in Group III. Motor response fluctuations were seen in five patients; all had end of dose wearing off, and two had on-off, as well.

Table 2 shows that the mean DA level in the normal control brains calculated for the whole GPe was 490 ng/g, and for the GPi 75 ng/g. There was no overlap of the single values between the two pallidal segments, and the mean values were

**Table 1** Summary of clinical features in eight Parkinson disease cases

Case no.	Sex	Age at onset, y	Age at death, y	Duration of MDCS follow-up, y	Motor features
1	M	56	74	17.0	Akinetic/rigid
2	F	69	78	4.9	Akinetic/rigid
3	M	80	89	6.0	Akinetic/rigid
4	F	67	79	10.4	Classical*
5	M	57	82	10.5	Classical*
6	M	53	86	21.0	Classical*
7	F	50	80	24.6	Tremor dominant
8	M	65	77	11.0	Tremor dominant

\*Classical = bradykinesia, rigidity, and tremor of comparable severity. MDCS = Movement Disorder Clinic Saskatoon.

**Table 2** Dopamine in globus pallidus in controls and Parkinson disease: comparison with caudate nucleus and putamen

	Dopamine, mean $\pm$ SEM in ng/g fresh tissue*		Percent of controls	p Value (vs controls)†
	Controls (n = 5)	Parkinson (n = 8)		
GPe	490 $\pm$ 128 (141-849)	89 $\pm$ 20 (30-192)	18	0.004
GPi	75 $\pm$ 12 (50-114)	37 $\pm$ 9 (14-91)	49	0.021
CN	4,833 $\pm$ 531 (3,381-6,610)	513 $\pm$ 164 (115-1,450)	11	<0.001
PUT	6,475 $\pm$ 568 (4,642-7,883)	105 $\pm$ 28 (27-245)	1.6	<0.001

\*Range in parentheses.

†Two-tailed t test.

GPe = external globus pallidus; GPi = internal globus pallidus; CN = caudate nucleus; PUT = putamen.

different ( $p = 0.027$ , paired  $t$  test). In the PD cases, the mean DA levels were reduced in the external (89 ng/g,  $p = 0.004$ ) and the internal (37 ng/g,  $p = 0.021$ ) pallidal segments. Relative to controls, the average loss of DA was greater in the GPe ( $-82\%$ ) than in the GPi ( $-51\%$ ). There was profound DA loss in the putamen ( $>98\%$ ) and less pronounced loss in the caudate nucleus ( $-89\%$ ) (table 2).

The regionally subdivided GPe and GPi DA levels in controls and PD cases are shown in table 3. In the control brains, the DA distribution in the GPe was uneven. The ventral portions had twice as much DA as the dorsal subdivisions (618 ng/g in the rostroventral vs 291 ng/g in the rostradorsal GPe). The means calculated for the whole ventral (rostral and caudal) GPe ( $623 \pm 171$  ng/g) and the whole dorsal (rostral and caudal) GPe ( $374 \pm 86$  ng/g) were different ( $p = 0.048$ , paired  $t$  test). In the GPi of the control cases, there was only a hint of a subregional DA pattern, with the mean DA levels in the rostral portions (89 and 99 ng/g) approximately 50% to 60% higher (nonsignificant) than the caudal portions (59 and 62 ng/g).

In PD, the GPe and GPi each had DA loss. In all GPe subregions DA loss was marked,  $-69\%$  in the rostroventral portion and  $-90\%$  in the caudodorsal subregion. In the GPi, the DA loss was marked only in the rostradorsal portion ( $p < 0.001$  vs controls). In the other GPi subregions, the reduction of DA was moderate, ranging between  $-37\%$  and  $-52\%$  (table 3).

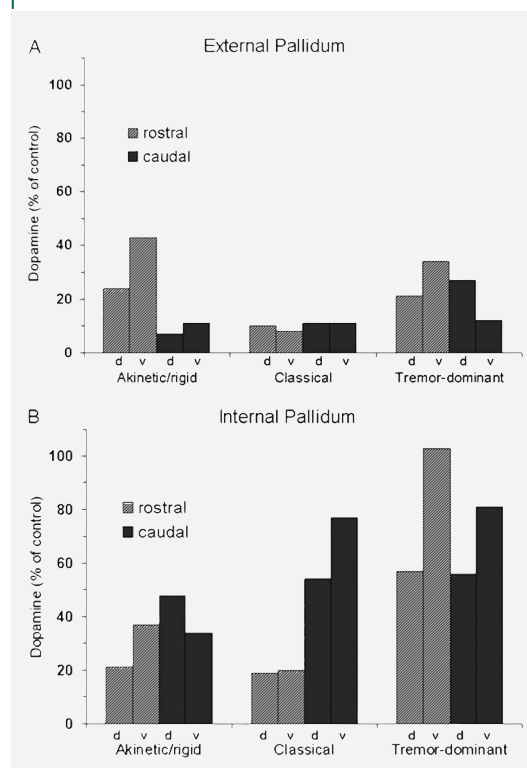
The figure shows the subregional DA (expressed in percent of control values) in the GPe and the GPi in the three subgroups of PD cases. In the GPe (figure, A) the reduction of DA was marked to severe throughout the subdivided structure ( $-57\%$  to  $-93\%$  DA loss) in each subgroup. The DA losses tended to be greater in the

caudal portions. The classic cases had very low DA (about  $-90\%$  loss) in all GPe subdivisions.

In contrast, in the GPi (figure, B), the subregional DA losses in the three symptom subgroups showed a differential pattern. In the rostral GPi, both dorsal and ventral regions, the loss of DA was substantially greater in the akinetic/rigid ( $-63\%$  and  $-79\%$ ) and the classic ( $-81\%$  and  $-80\%$ ) than in the tremor-dominant cases ( $-43\%$  and  $+3\%$ ). When the akinetic/rigid and the classic cases were considered together, the DA loss was greater ( $p = 0.013$ ) in the rostradorsal and the rostroventral ( $p = 0.003$ ) subdivisions compared to the tremor dominant cases. In the caudal subdivision of the GPi, the DA losses followed a different pattern. All three PD subgroups had only a moderate DA loss (by about 50%) in the dorsal portion. In the ventral subdivision of the caudal GPi, however, the two patient groups manifesting tremor—the classic and tremor-dominant cases—had DA levels close to the control values (77% and 81% of controls), being more than twice the DA levels observed in the akinetic/rigid group.

In the caudate, the greatest DA losses were found in classic cases ( $-97.5\%$ ) followed by aki-

**Figure** Subregional pallidal dopamine (DA) in three symptom subgroups with Parkinson disease



The columns indicate the average DA values in percent of the corresponding controls. d = dorsal; v = ventral subdivisions.

**Table 3** Subregional dopamine (DA) in external and internal globus pallidus in controls and Parkinson disease (PD)

	DA, mean $\pm$ SEM in ng/g fresh tissue			p Value*
	Controls (n = 5)	PD (n = 8)	% DA loss in PD	
<b>External globus pallidus</b>				
<b>Rostral</b>				
Dorsal	291 $\pm$ 82	52 $\pm$ 17	-82	0.004
Ventral	618 $\pm$ 201	172 $\pm$ 55	-69	0.02
<b>Caudal</b>				
Dorsal	452 $\pm$ 115	44 $\pm$ 14	-90	0.002
Ventral	619 $\pm$ 164	74 $\pm$ 10	-88	0.002
<b>Internal globus pallidus</b>				
<b>Rostral</b>				
Dorsal	89 $\pm$ 12	26 $\pm$ 7	-71	<0.001
Ventral	99 $\pm$ 23	47 $\pm$ 14	-52	0.06 (NS)
<b>Caudal</b>				
Dorsal	59 $\pm$ 14	31 $\pm$ 6	-47	0.08 (NS)
Ventral	62 $\pm$ 23	39 $\pm$ 10	-37	0.18 (NS)

\*Two-tailed t test.

netic/rigid (-89.4%) and the tremor dominant cases (-77.1%). In the putamen, the classic and akinetic/rigid cases had very severe DA losses (-99%), and tremor dominant cases had less pronounced (loss of -96.5%) though significant DA loss, indicating that the nigrostriatal disease process in the tremor dominant cases was less severe than in akinetic rigid and the classic cases.

**DISCUSSION** Subregional DA patterns in two pallidal segments in the normal human brain and in the brain of patients with PD with different combinations of motor symptoms have not been reported previously. Our data show that in PD both segments of the globus pallidus suffer significant DA loss. DA reduction was marked to severe in the subdivisions of the GPe and moderate in the subdivided GPi. We provide tentative evidence for a difference in the subregional DA in the ventral GPi between cases with resting tremor (tremor-dominant and classic PD) and akinetic-rigid cases.

As originally proposed,<sup>8</sup> the DA in the human pallidum is contained in a nigropallidal projection both in a separate nigropallidal pathway and in fiber collaterals of the nigrostriatal DA pathway<sup>11-13</sup> (for review, see Björklund and Lindvall<sup>22</sup>). The neurons in the human pallidum also express (moderately dense) DA receptors, D1 mainly in the GPi, and D2 in the GPe.<sup>23</sup> Recent neurophysiologic, pharmacologic, and behavioral studies have established pallidal DA as a neuro-

transmitter/modulator within these pivotal striatal output stations.<sup>24,25</sup>

As in earlier studies,<sup>26-29</sup> we found about sixfold higher DA levels in the whole GPe compared with the whole GPi. This study provides quantitative data on the discrete subregional distribution of DA in both pallidal segments of the normal human brain. In the GPe, DA was unevenly distributed, with the ventral subdivision having about twofold higher levels than the dorsal subdivision (table 3). This difference may be of functional significance because the ventral GPe is thought to receive the main (GABAergic) innervation from the sensorimotor putamen.<sup>30</sup> In the GPi of the normal control brains, the DA was more evenly distributed with only slightly higher levels in the rostral compared with the caudal subdivision.

Several histochemical studies have confirmed the existence, in the human brain, of terminal axon arborizations with varicosities in both pallidal segments, consistent with DAergic innervation of these structures.<sup>11-13,31,32</sup> In contrast to the biochemical reports, including this study, the histochemical studies observed DAergic innervation to be equally dense in both pallidal segments. The reason for this discrepancy is not clear. One possibility for the higher GPe DA in the biochemical studies is the higher density of nigrostriatal DA fibers coursing through the GPe to reach the putamen. That is unlikely as there is no corresponding gradient of DA's metabolite homovanillic acid.<sup>33</sup> Additionally, we processed GP samples carefully to dissect the major fiber bundles passing through the GPe. More likely, the recently discovered small islands of apparent neostriatal tissue which are scattered throughout the GPe but not the GPi<sup>13</sup> might contain disproportionate amounts of DA observed in the biochemical studies compared to that detected in the histochemically immunoreactive material studied.

Our study shows that in PD, both pallidal segments suffer highly significant DA loss. The mean DA loss was marked to severe in the GPe (-82%) and moderate in the GPi (-51%) (table 2). These results confirm the study by Ploska et al.<sup>26</sup> as well as earlier observations in the undivided pallidum.<sup>34,35</sup>

The marked severity of DA loss throughout the GPe could be the result of the severe loss of the (DA poor) nigrostriatal fibers of passage combined with the loss of pallidal collaterals of the nigrostriatal DA fibers, including the DAergic innervation of the islands of apparent neostriatal tissue found scattered throughout the GPe.<sup>13</sup> Since the neurons of these islands most likely establish functional connections

with the surrounding intrinsic GPe neurons, the loss of their DAergic innervation in PD may be of some functional consequence.

The loss of DA in the subregionally divided GPi, with one exception (rostradorsal) in PD was moderate in degree, ranging between  $-37\%$  and  $-52\%$  in contrast to the profound DA loss in the GPe (and the striatum). This suggests that the DA fibers innervating the GPi are separate from both the nigrostriatal fibers and those innervating the GPe and degenerate independently of the latter. The only portion of the GPi with marked DA loss ( $-71\%$ ) was the rostradorsal subregion which appears to receive its striatal GABAergic innervation from the head of the caudate nucleus.<sup>30</sup>

In view of the demonstrated physiologic actions of DA on pallidal neuronal activity as well as the effects on motor behavior of intrapallidal DA and DA blockers<sup>24,25</sup> application, it is reasonable to assume that loss of pallidal DAergic control would contribute to the motor deficits in PD. It is not possible to decide which of the two pallidal segments is more important in this respect. Some evidence suggests that pallidal DA may participate in the phenomenon of functional compensation in the face of the profound striatal DA loss in the early stage of the clinically overt disorder. In the MPTP-treated primate with stable parkinsonian symptoms there was marked pallidal DA depletion. However, the pallidal DA levels were normal in animals that were asymptomatic but had very marked striatal DA deficit.<sup>36</sup> It was suggested that pallidal DA is important for the functional compensation in early PD. This has been recently confirmed in a PET study.<sup>37</sup> Clinically mild PD cases demonstrated a striking discrepancy between the markedly reduced <sup>18</sup>F-dopa uptake in the striatum and normal uptake in the GPi.<sup>37</sup> In contrast, patients with severe PD symptoms had reduced <sup>18</sup>F-dopa uptake in both the striatum and the GPi.<sup>37</sup> These authors interpreted their observation as indicating “a compensatory up-regulation in the nigropallidal dopamine projection to the GPi” in early PD cases.

Our patients included three akinetic/rigid cases in whom tremor was not clinically evident and five cases with prominent tremor, either as part of the cardinal symptoms (three classic PD cases) or as the dominant PD feature (two tremor-dominant cases). In all three symptom subgroups, all subdivisions of the GPe had significantly reduced DA levels (figure, A). The DA loss was very marked (about 90%) in the classic cases, affecting

uniformly all subdivisions of the GPe. The same degree of DA loss was also present in the caudal GPe subdivisions in the akinetic/rigid group. In contrast, the rostral GPe subdivisions in the akinetic/rigid cases as well as all GPe subdivisions in the tremor-dominant cases were distinctly less affected, with the DA losses ranging between  $-57\%$  and  $-83\%$ . These subregional DA losses may be clinically relevant in view of the recent experimental studies in nonhuman primates indicating that the anatomically defined associative, limbic, and motor subdivisions of the GPe participate in several aspects of attentional motivational and motor behaviors.<sup>38,39</sup>

In the GPi, the subregional DA loss in the three symptom subgroups differed in several respects from the DA patterns found in the GPe (figure, B). The akinetic/rigid cases had marked DA loss in the dorsal and ventral portions of the rostral GPi, as well as in the ventral portion of the caudal subdivision. The classic cases had marked reduction of DA in the ventral and dorsal portions of the rostral GPi. The tremor-dominant cases had (moderate) loss of DA (about  $-50\%$ ) in the dorsal portions of the rostral and caudal GPi. From a clinical point of view, a striking observation was that the DA in the rostral GPi (both dorsal and ventral portions) was significantly lower in the akinetic/rigid and the classic cases as a group, compared to the tremor-dominant cases (figure, B). Whether this implicates the rostral GPi DA in some symptoms common to both these subgroups must, however, remain an open question. Possible involvement of the rostral GPi in non-motor symptoms is suggested by the demonstration that in the primate, GPi neurons responding to movement (arm, leg) have been localized to the central and caudal parts of the nucleus, conspicuously avoiding the rostral GPi.<sup>40</sup> On the other hand, in patients undergoing neurosurgery, motor manifestations affecting the region of the head, e.g., oculogyric and pharyngeal phenomena, were found to respond better to lesions of the rostral GPi than to other GPi locations.<sup>41</sup>

It is important to note that the DA losses observed in the three symptom subgroups bore no relation to the severity of the parkinsonian disease process, as judged by the degree of the DA loss in the putamen. Thus, although the disease process was less advanced in the tremor-dominant group (226 ng/g DA still remaining in the putamen) than in the akinetic/rigid (62 ng/g putaminal DA) and the classic cases (66 ng/g putaminal DA), the considerable intergroup overlap

of the pallidal DA losses (figure, A and B) did not match this putaminal DA pattern.

Functionally more important is the observation that in five of our eight PD cases, having resting tremor as the common feature, i.e., the classic and tremor-dominant cases, the DA in the ventral GPi was at, or close to, control levels. Viewed in the context of the available neurosurgical literature, this finding suggests the possibility of a direct relationship between the DAergic mechanisms in the ventral GPi and the presence of resting tremor in PD.

How could the selective sparing of the ventral GPi DA be related to the resting tremor in PD? The ventral GPi is the motor region of the nucleus, which receives its major innervation from the sensorimotor putamen.<sup>42,43</sup> In PD, these inhibitory GABAergic putaminal fibers (of the so-called direct pathway) are thought to be underactive.<sup>6,7</sup> If we assume that in the ventral GPi, the putaminal GABAergic and the nigral DAergic projections converge on the same neuronal subpopulations, the influence of both systems on the intrinsic GPi neurons will be equally reduced in the akinetic/rigid cases. By contrast, in the classic and the tremor-dominant cases the underactivity of the GABA neurons, according to our data, is not accompanied by reduced influence of the (intact) DA neurons. We hypothesize that the resulting functional neurotransmitter imbalance favoring the (most probably excitatory) DAergic activity underlies, or contributes to, the symptom of resting tremor in these two subgroups—classic and tremor dominant cases.

Human experimental and neurosurgical literature indicates that the GPi plays an important role in the motor symptoms of PD. Cells firing rhythmically at the same frequency (4 to 6 HZ) as the resting tremor have been identified in the GPi in PD cases.<sup>44</sup> Indeed, GPi surgery and deep brain stimulation can relieve all the major motor symptoms of PD, with consistent benefit to resting tremor.<sup>45-47</sup> The fact that it is the ventral, especially the caudoventral (posteroventral), region of the GPi that is the main surgical target area in PD adds credibility to our observations.

Our findings may also be relevant to some pathologic and clinical observations. In the course of parkinsonism, tremor may decrease after reaching a peak,<sup>48</sup> suggesting progression of pathology (to include the DA fibers to ventral GPi?) as a possible factor. Tremor is relatively less common in progressive supranuclear palsy and multiple system atrophy<sup>1,49</sup> where the pathology almost always involves the pallidum, including the GPi. It has been reported that at the start of levodopa (or DA agonist) ther-

apy, tremor may increase in some cases,<sup>50-53</sup> or be acutely precipitated by a dose of levodopa in some patients with prominent rigidity and bradykinesia.<sup>54</sup> A sudden, levodopa-induced rise in local DA levels, especially in the ventral GPi, as the cause of these transient tremorogenic effects of levodopa in some patients with PD would be consistent with our biochemical observations.

We suggest that in PD the subregional DA losses observed in this study in both the pallidal segments, together with severe putaminal DA loss, are substantial enough to contribute to the overall dysfunction of the basal ganglia motor circuits involved in this disorder. We interpret the sparing of the DAergic innervation of the ventral GPi specifically in the cases having resting tremor as their common denominator, i.e., the tremor dominant and the classic PD cases, as indicative of an involvement of the ventral GPi DA in the pathophysiology of the resting tremor in PD.

Studies of human brains were critical in identifying DA deficiency in PD.<sup>34</sup> There is, however, paucity of human brain studies dealing with different motor subtypes of PD. We attribute that to the scarcity of suitable study material as the motor features in PD may change with time.<sup>48</sup> A major objective of this study was to study patients in whom the motor subtype remained unchanged through the entire course of illness. In spite of small number of cases the data in this study are robust and are consistent with other literature evidence.

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