

Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder

Comparison with Parkinson's disease and controls

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Summary

Rapid eye movement (REM) sleep behaviour disorder (RBD) is characterized by complex behaviour during REM sleep. The aetiology of this disorder is still unknown, but a recent study showed an association between RBD and Parkinson's disease. We therefore studied striatal postsynaptic dopamine D₂ receptor density with [¹²³I](S)-2-hydroxy-3-iodo-6-methoxy-(1-ethyl-2-pyrrolidinylmethyl) benzamide ([¹²³I]IBZM) and the striatal presynaptic dopamine transporter with (N)-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane ([¹²³I]IPT) using single-photon emission computed tomography (SPECT) in patients with idiopathic RBD. We compared the [¹²³I]IPT-SPECT results of five patients with polysomnographically confirmed idiopathic RBD with the [¹²³I]IPT-SPECTs of seven age- and sex-matched controls without a history of sleep disorders, and of 14

patients with Parkinson's disease (Hoehn and Yahr stage I). All RBD patients had significantly reduced striatal [¹²³I]IPT binding compared with the controls (RBD: right, 2.94 ± 0.32 , left, 3.03 ± 0.41 ; controls: right, 4.41 ± 0.17 , left, 4.34 ± 0.21 ; $P = 0.003$), but significantly higher striatal [¹²³I]IPT binding compared with the striatum contralateral to the symptomatic body side of the Parkinson's disease patients (Parkinson's disease: ipsilateral, 3.17 ± 0.36 , $P = 0.298$; contralateral, 2.51 ± 0.31 , $P = 0.019$). Uptake of [¹²³I]IBZM was not significantly different in the RBD group compared with the controls. This study demonstrates that [¹²³I]IPT-SPECT is a useful diagnostic tool in RBD and that reduced striatal dopamine transporters may be a pathophysiological mechanism of idiopathic RBD. (Results are given as mean \pm standard deviation.)

Keywords: presynaptic dopamine transporter; postsynaptic D₂ receptor; REM sleep behaviour disorder; Parkinson's disease

Abbreviations: [¹²³I]IBZM = [¹²³I](S)-2-hydroxy-3-iodo-6-methoxy-(1-ethyl-2-pyrrolidinylmethyl) benzamide; [¹²³I]IPT = [¹²³I](N)-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane; RBD = REM sleep behaviour disorder; REM = rapid eye movement; ROI = region of interest; SPECT = single-photon emission computed tomography

Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) involves complex behaviour and a loss of skeletal muscle atonia during REM sleep. This parasomnia was first described by Schenck and colleagues (Schenck *et al.*, 1986). The minimal diagnostic criteria for RBD, as defined by the International Classification of Sleep Disorders, include movements of the limbs or body associated with dream mentation, and at least one of the following criteria: potentially harmful sleep behaviour; dreams that appear to be acted out; and sleep behaviour that disrupts sleep continuity (American Sleep Disorders Association, 1997).

Patients often recall aggressive or violent dreams and sometimes injure their bed partner or themselves during episodes of RBD.

The underlying cause of RBD is still unknown. Experimental lesions of the dorsolateral pontine tegmentum in animals were reported to cause a loss of normal REM muscle atonia (Jouvet and Delorme, 1965). A recent prospective study showed that 38% of the patients with RBD eventually developed Parkinson's disease (Schenck *et al.*, 1996). Another study showed that clinical symptoms of RBD preceded the onset of multiple system atrophy by

>1 year in 44% of the patients examined (Plazzi *et al.*, 1997). Patients with Parkinson's disease consistently have reduced numbers of presynaptic dopamine transporters and normal postsynaptic D₂ receptor binding (Tatsch *et al.*, 1997), whereas patients with multiple system atrophy often show reduced numbers of presynaptic dopamine transporters and postsynaptic dopamine D₂ receptor binding (Schulz *et al.*, 1994). We performed [¹²³I](N)-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane ([¹²³I]IPT)- and [¹²³I](S)-2-hydroxy-3-iodo-6-methoxy-(1-ethyl-2-pyrrolidinylmethyl) benzamide ([¹²³I]IBZM)-SPECT (single-photon emission computed tomography) studies in patients with idiopathic RBD to determine whether this parasomnia is associated with an abnormality of the presynaptic dopamine transporters or the postsynaptic dopamine D₂ receptors.

Methods

Study population

Five patients (four men, one woman; mean age 68.5 ± 7.5 years, range 60–77 years) with polysomnographically confirmed RBD, 14 age- and sex-matched healthy controls (11 men, three women; mean age 64.6 ± 4.8 years, range 55–71 years) without a history of sleep disorders and 14 Parkinson's disease patients (10 men, four women; mean age 50.3 ± 9.9 years, range 36–68 years) participated in the study. The SPECT imaging results of the RBD group were compared with those of the control group and the [¹²³I]IPT-SPECT results of a group of 14 Parkinson's disease patients.

All patients diagnosed with idiopathic RBD had a history of several years of violent behaviour during sleep associated with screaming, aggressive dream content, and self-injury or injury of the bed partner. Only one of the patients reported a family history of parasomnia (his father has reportedly had violent behaviour during sleep), and all patients were normal on neurological examination. Our controls did not have polysomnographies, and significant sleep disorders including RBD were excluded by individual interviews (Comella *et al.*, 1998). The existence of REM sleep without atonia and without locomotion could not be excluded. The RBD and control group were not significantly different in age and sex distribution. The Parkinson's disease group was significantly younger than the controls and the RBD group.

All 14 Parkinson's disease patients fulfilled the clinical criteria of steps 1 and 2 established by the Parkinson's Disease Society brain bank (Hughes *et al.*, 1992), indicating that all patients had at least bradykinesia and at least one of the other features of Parkinson's disease, such as resting tremor, rigidity, and impairment of postural reflexes. Considering the prospective supportive criteria, all Parkinson's disease patients had a progressive disorder, resting tremor, unilateral onset and/or persisting asymmetry and were rated as Hoehn and Yahr stage I. Disease duration was 20 ± 11 months (range 12–48 months). Our patients

with Parkinson's disease had been part of another study that looked systematically for [¹²³I]IPT-SPECT changes in Parkinson's disease (Schwarz *et al.*, 2000).

For each tracer, a separate group of age- and sex-matched controls with no known sleep disorder was used for comparison. The IPT data of the RBD and Parkinson's disease group were compared with those of seven age- and sex-RBD-matched controls (five men, two women; mean age 63.0 ± 6.4 years, range: 55–71 years). Another group of seven age- and sex-RBD-matched healthy controls (six men, one woman; mean age 66.1 ± 2.0 years; range 63–68 years) was used for comparison with the RBD patients' [¹²³I]IBZM data. None of the controls had a history of violent behaviour during sleep or any other significant sleep disturbance.

Four patients had normal cranial MRIs. A 77-year-old woman showed multiple microvascular white matter lesions in both hemispheres.

The study was approved by the ethics committee of the University of Munich, and informed consent was obtained from each subject. None of the controls or patients (RBD and Parkinson's disease) was pretreated with dopaminergic agents. Four RBD patients were taking the following medications at the time of the study: (patient 1) 400 mg carbamazepine daily, discontinued 5 days before the study; (patient 2) bezafibrate, fendiline, beta-acetyldigoxin, piracetam, ginkgo biloba; (patient 3) 500 mg valproic acid daily, 0.5 mg clonazepam daily; the latter was discontinued 2 days before the study; (patient 4) propiverine. One patient received no medication.

[¹²³I]IPT-SPECT

IPT is an analogue of cocaine with high binding affinity ($K_i = 0.2$ nM) for the dopamine transporter (Kung *et al.*, 1995). The IPT precursor was radiolabelled according to a method described in detail previously (Kung *et al.*, 1995; Mozley *et al.*, 1996). [¹²³I]Sodium iodide was purchased from a commercial vendor (Cygne BV, Eindhoven, The Netherlands). The radionuclide purity was >99.9%, and the specific activity was calculated as 2×10^{17} Bq/mol. The final product was analysed for purity before injection. 120 MBq of radioactive [¹²³I]IPT was injected into an antebrachial vein of the patients and controls. The protocols used for the acquisition and processing of [¹²³I]IPT-SPECT data have been described in detail previously (Mozley *et al.*, 1996; Tatsch *et al.*, 1997). A triple-headed gamma camera equipped with high-resolution fan beam collimators (Picker Prism 3000, Picker International, Cleveland, OH, USA) was used for acquisition. The acquisition parameters were a rotational radius of 12.8–13 cm, a 20% energy window centred on 159 keV, 120 projection angles over 360°, and a 128 × 128 matrix. Data collection started 90 min after injection and lasted ~30 min (45 s per projection). The projection images were reconstructed by filtered back-projection. A three-dimensional postprocessing filter (low-pass filter) was then

applied. For uniform attenuation correction, Chang's first-order method was used. Images were resliced by drawing a line connecting the anteriormost aspect of the frontal pole to the posteriormost aspect of the occipital pole, which approximates the line connecting the anterior and posterior commissures. To assess specific tracer uptake in the striatum, we used the region of interest (ROI) technique. Mean specific activity in the basal ganglion regions was calculated by subtracting the mean counts per pixel in the background (BG) from the mean counts per pixel in the basal ganglion region and dividing the result by the mean number of counts per pixel in the background [(ROI - BG)/BG]. Templates were used for defining the striatum (S), caudate (C) and putamen (P) ROIs. The size and shape of the templates were established and optimized using the data of the control group. The non-specific background activity was estimated by drawing a large ROI around the entire supratentorial brain on the slices containing the basal ganglia, but excluding the basal ganglia and the thalamus. This type of large ROI was preferred over small ROIs covering only brain tissue known to be relatively free of dopamine transporters (e.g. occipital cortex, cerebellum), as evaluations based on small ROIs may be more susceptible to artefacts caused by low and heterogeneous count rates in areas of non-specific IPT binding. Data for each patient were evaluated in the six consecutive transverse slices (slice thickness 2.27 mm) showing the highest tracer accumulation in the basal ganglia. Results are given as the arithmetic mean of the six slices (thickness ~14 mm).

[¹²³I]IBZM-SPECT

Striatal dopamine D₂ receptor binding was assessed using [¹²³I]IBZM-SPECT. IBZM binding was assessed 2 h after intravenous injection of 185 MBq of the ligand. For acquisition, a triple-headed gamma camera equipped with specially designed collimators for ¹²³I (Münzing *et al.*, 1996) was used (Multispect 3, Siemens, Munich, Germany). The acquisition parameters were a rotational radius of 12.8–13 cm, a 20% energy window centred on 159 keV, 90 projection angles over 360°, and a 128 × 128 matrix. The acquisition time was 80 s per projection. Images were reconstructed by filtered back-projection using a Butterworth filter. The transverse slices were corrected for attenuation according to Chang's method. For the semiquantitative evaluation of specific tracer uptake, ROIs were placed over the basal ganglia (isocontour ROIs with a threshold of 80% of the striatal maximum) and the frontal cortex (irregular ROIs). Mean specific activity in basal ganglion regions was calculated in the two transverse slices showing the highest tracer uptake (thickness ~14 mm) by subtracting the mean counts per pixel in the frontal cortex (FC) from the mean counts per pixel in the basal ganglion region and dividing the result by the mean counts per pixel in the FC [(ROI - FC)/FC].

Sleep studies

All patients with RBD underwent polysomnographies to confirm the previously clinically suggested diagnosis of RBD. A digital system (Brainlab, Schwarzer, Munich, Germany) was used for recording the polysomnograms (PSGs). The study began around 10 p.m. and ended at 6 a.m.; during this time EEGs, EOGs, and mental and submental EMGs were recorded. The surface EMGs of both anterior tibial muscles were recorded as described by Coleman (Coleman, 1982). The oronasal airflow was recorded via thermistors mounted over the nose and mouth. The thoracic and abdominal respiratory movements were recorded by impedance plethysmography. Arterial oxygen saturation was measured continuously via a non-invasive infrared finger probe. The electrocardiogram was recorded continuously between the forearms. Sleep staging followed the recommendations of Rechtschaffen and Kales (Rechtschaffen and Kales, 1968). Apnoea and hypopnoea were defined according to a protocol published in detail recently (Eisensehr *et al.*, 1998). Arousal scoring and periodic limb movement scoring followed published guidelines (Atlas Task Force of the American Sleep Disorders Association, 1992, 1993).

Three patients had their polysomnogram 2 weeks and two patients had theirs 18 months before their SPECT examinations. No patient showed significant sleep-disordered breathing during the night of the polysomnogram. All patients had abnormal REM sleep with continuous increased chin, leg and arm EMG activity during REM episodes. One patient had been treated for 3 years with nasal continuous positive airway pressure (7 cm H₂O) for excessive daytime sleepiness due to obstructive sleep apnoea syndrome at the time of the study. We rescored his former polysomnogram and found REM sleep without atonia; this had been ignored when the diagnosis of obstructive sleep apnoea syndrome was made. Two patients showed >10 periodic limb movements per hour of total sleep time (18 and 58/h).

Data presentation and statistics

Data were analysed using SPSS version 7.5 for Windows. They are presented as mean and standard deviation of the mean if not stated otherwise. The data were tested for normal distribution with the Kolmogorov–Smirnov test. Data points between the three study groups (RBD versus controls versus Parkinson's disease) were compared using the χ^2 test for comparison of sex distribution, the Mann–Whitney *U*-test for non-normally distributed data and the *t*-test for normally distributed data. *P* < 0.05 was considered significant.

Results

[¹²³I]IPT-SPECT

All RBD patients had [¹²³I]IPT-SPECT results outside the normal range. The RBD group had significantly reduced striatal IPT uptake ratios compared with the control group

Table 1 Results of [¹²³I]IPT-SPECT (IPT binding ratio)

		RBD (n = 5)	Controls (n = 7)	PD	
				Contralateral (n = 14)	Ipsilateral (n = 14)
Striatum	Right	2.94 ± 0.32	4.41 ± 0.17 <i>P</i> = 0.003	2.51 ± 0.31 <i>P</i> * = 0.019	3.17 ± 0.36 <i>P</i> * = 0.298
	Left	3.03 ± 0.41	4.34 ± 0.21 <i>P</i> = 0.003	<i>P</i> ** = 0.014	<i>P</i> ** = 0.391
Caudate	Right	3.32 ± 0.24	4.76 ± 0.15 <i>P</i> = 0.003	3.20 ± 0.38 <i>P</i> * = 0.391	3.76 ± 0.48 <i>P</i> * = 0.087
	Left	3.44 ± 0.45	4.72 ± 0.28 <i>P</i> = 0.003	<i>P</i> ** = 0.298	<i>P</i> ** = 0.186
Putamen	Right	2.81 ± 0.44	4.35 ± 0.19 <i>P</i> = 0.003	1.79 ± 0.34 <i>P</i> * < 0.0001	3.71 ± 0.32 <i>P</i> * = 0.823
	Left	2.86 ± 0.46	4.32 ± 0.18 <i>P</i> = 0.003	<i>P</i> ** < 0.0001	<i>P</i> ** = 0.754
Putamen : Caudate ratio	Right	0.85 ± 0.07	0.92 ± 0.02 <i>P</i> = 0.106	0.57 ± 0.08 <i>P</i> * < 0.0001	0.73 ± 0.08 <i>P</i> * = 0.002
	Left	0.83 ± 0.08	0.92 ± 0.04 <i>P</i> = 0.048	<i>P</i> ** < 0.0001	<i>P</i> ** = 0.019

Data are mean ± standard deviation. *n* = number of patients; PD = patients with Parkinson's disease at Hoehn and Yahr stage I; Ipsilateral = striatal IPT binding reflecting the asymptomatic side of the body; Contralateral = striatal IPT binding contralateral to the symptomatic side of the body; *P* = comparison of RBD with controls; *P** = comparison of the right side of RBD with Parkinson's disease; *P*** = comparison of the left side of RBD with Parkinson's disease.

Striatal IPT uptake

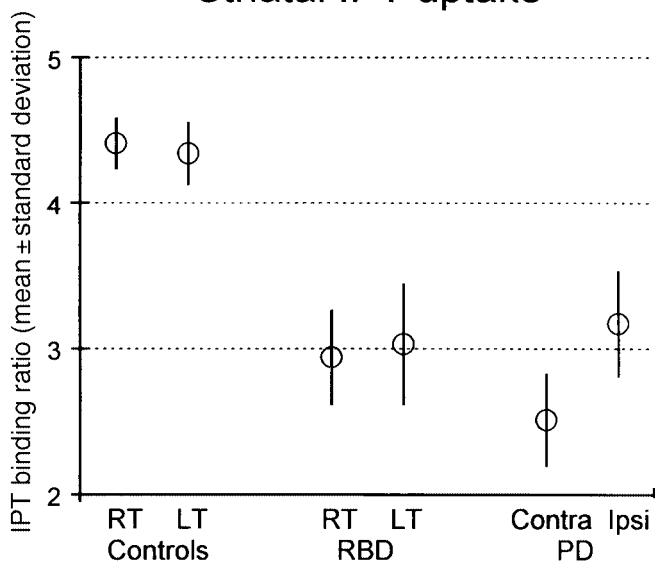


Fig. 1 Striatal presynaptic IPT-binding ratio of patients with RBD and Parkinson's disease (Hoehn and Yahr stage I) and controls. Values are mean ± standard deviation. RT = right; LT = left; Contra = striatal IPT binding contralateral to the symptomatic side of the body; Ipsi = striatal IPT binding corresponding to the asymptomatic side of the body.

(Table 1 and Fig. 1). RBD patients showed significantly higher striatal IPT binding than that in the striatum contralateral to the clinically symptomatic side in Parkinson's disease patients in Hoehn and Yahr stage I (Table 1 and Fig. 1). Striatal IPT binding in RBD patients was not significantly different from IPT binding in the ipsilateral striatum of Parkinson's disease

patients, corresponding to the so-far unaffected body side (Table 1 and Fig. 2).

[¹²³I]IBZM-SPECT

Postsynaptic dopamine-D₂ receptors were reduced in the RBD patient group, but the differences were not statistically significant compared with controls (RBD patients, right = 0.62 ± 0.06, left = 0.60 ± 0.10; controls, right = 0.68 ± 0.08, left = 0.68 ± 0.07; *P* = 0.202).

Discussion

All our patients with RBD had markedly reduced striatal dopamine transporters compared with healthy controls. There were no abnormalities in the neurological examinations of controls and RBD that would suggest further brain pathology.

Findings from experimental lesion studies in animals and MRI studies in secondary RBD suggest that degenerated brainstem nuclei are the anatomical basis for RBD (Hendricks *et al.*, 1982; Culebras and Moore, 1989). Culebras and Moore found small vascular periventricular lesions in five of six patients with RBD (Culebras and Moore, 1989). Small vascular lesions, however, are common in older patients with risk factors for stroke, and yet presumably only a few develop RBD. Four of our patients had normal cranial MRIs and only one showed non-specific microvascular white matter lesions in both hemispheres. No brainstem lesions were detected by MRI in our patients with RBD.

There are several links between RBD and Parkinson's disease. About one-third of patients with RBD develop

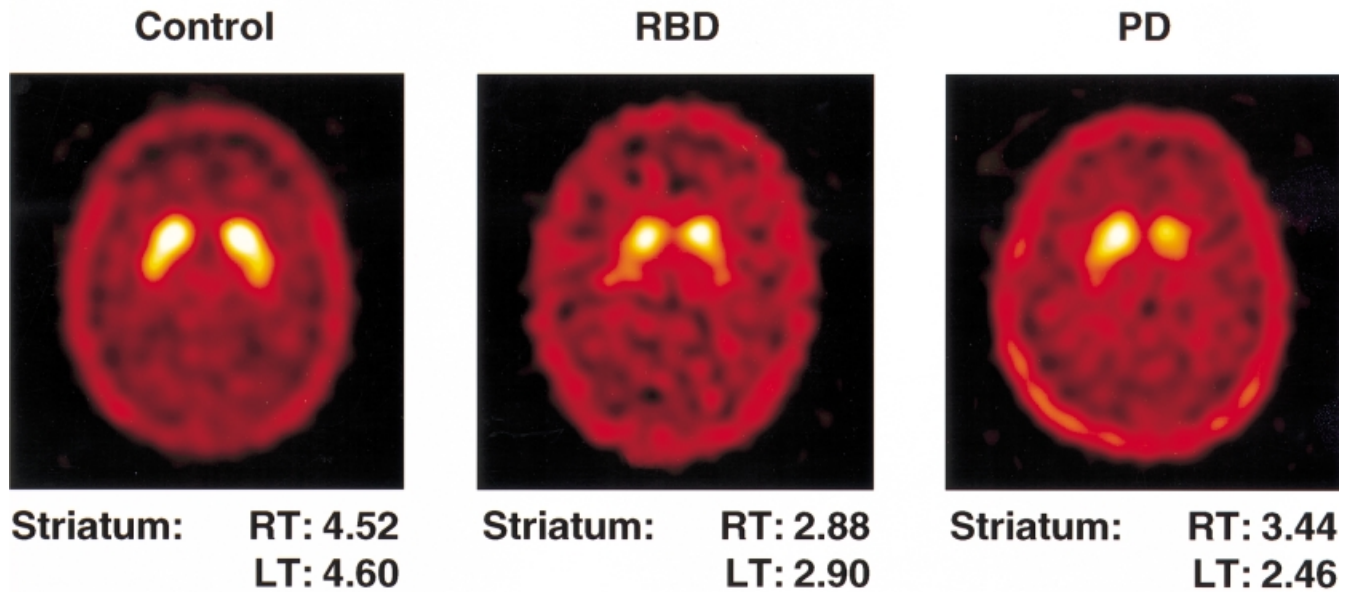


Fig. 2 The [^{123}I]IPT-SPECT of one patient with RBD, one patient with Parkinson's disease (Hoehn and Yahr stage I) and one control subject. Binding ratios are given below the [^{123}I]IPT-SPECTs. Note the bilaterally reduced IPT binding ratio in the RBD patient, whereas in the Parkinson's disease patient the reduction is asymmetrical, being more pronounced contralateral to the symptomatic body side of the patient. RT = right; LT = left.

Parkinson's syndrome later in life (Schenck *et al.*, 1996) and ~15% of patients with Parkinson's disease suffer from RBD (Comella *et al.*, 1998). In Parkinson's disease, the putamen is commonly more affected than the caudate (Tatsch *et al.*, 1997), which is also true for our RBD patients. The putamen : caudate ratio was slightly (on the left side significantly) lower in RBD patients than in the controls, but significantly higher on both sides in RBD than in Parkinson's disease patients. Striatal IPT binding and putamen : caudate ratios in RBD show a tendency towards IPT binding reflecting the clinically asymptomatic side in Parkinson's disease. Striatal IPT uptake in RBD was lower than in the controls but higher than in Parkinson's disease (Schwarz *et al.*, 2000). IPT binding contralateral to the clinically symptomatic side in Parkinson's disease was significantly lower than IPT binding in RBD.

Rye hypothesized that the GABAergic output of the basal ganglia targets the glutamatergic retrorubral field and/or neurons of the midbrain extrapyramidal area, which, in turn, activates the ventromedial medullary zone, which promotes REM atonia (Rye, 1997). Dopamine cell loss in the substantia nigra occurs transiently or is persistent in pathological states such as Parkinson's disease (Vitek *et al.*, 1993). One would expect heightened phasic discharge of the internal segment of the globus pallidus secondary to dopamine cell loss in the substantia nigra to inhibit the midbrain extrapyramidal area excessively, thereby allowing the expression of movements that overcome REM atonia. This hypothesis is supported by clinical experience in individual cases which shows that excessive nocturnal movements in Parkinson's disease (Rye and Bliwise, 1997) can be reversed by removing excessive inhibition of the midbrain extrapyramidal area by pallidotomy (Vitek *et al.*, 1993).

If it is a reduction in the number of striatal dopaminergic neurons that causes RBD, why do all patients with Parkinson's disease not also suffer from RBD? In Parkinson's disease, there is additional degeneration of brainstem neurons that play significant roles in the control of behavioural state, particularly the brainstem monoaminergic nuclei (Jellinger, 1991). There are two different glutamatergic receptors in the dorsolateral pons and the nucleus magnocellularis: one promotes REM sleep without atonia and with locomotion, and the other promotes atonia in REM sleep (Lai and Siegel, 1990, 1991). In Parkinson's disease, additional degeneration of brainstem neurons that promote REM sleep without atonia might therefore cancel the effect of heightened phasic discharge of the internal segment of the globus pallidus secondary to dopamine cell loss in the substantia nigra. Conversely, additional degeneration of brainstem neurons that promote REM sleep with atonia might promote RBD. This hypothesis might explain why only certain patients with Parkinson's disease are affected by RBD, even if a reduced number of striatal dopaminergic neurons without further brainstem lesions promotes RBD. The observation that multiple system atrophy is frequently associated with RBD (Plazzi *et al.*, 1997) also supports the degenerative concept.

Our results demonstrate that reduced numbers of striatal dopamine transporters are relevant not only in patients with Parkinson's disease and Parkinson's syndrome, but also in RBD. IPT-SPECT might be a useful tool in the diagnosis of RBD. The reduction of striatal dopaminergic neurons may play a role in the development of idiopathic RBD, or RBD may be the initial manifestation of an otherwise asymptomatic phase of Parkinson's disease. Follow-up of these patients is needed.

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