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# Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system

Philippe Remy,[1,2] Miroslava Doder,[2] Andrew Lees,[3] Nora Turjanski[2] and David Brooks[2]

[1]*CNRS-CEA URA2210, Service Hospitalier Frédéric Joliot, CHU Henri Mondor et Faculté de Médecine Paris 12, France* [2]*Faculty of Medicine, Hammersmith Hospital, Imperial College-MRC Clinical Sciences Centre and Division of Neuroscience and* [3]*Institute of Neurology, Queen Square, London, UK*

*Correspondence to: Philippe Remy, CNRS-CEA URA2210, Service Hospitalier Frédéric Joliot, 4, place du Général Leclerc, 91401 Orsay cedex, France.*
*E-mail: remy@shfj.cea.fr*

## Summary

**The reason for the high frequency of depression and anxiety in Parkinson's disease is poorly understood. Degeneration of neurotransmitter systems other than dopamine might play a specific role in the occurrence of these affective disorders. We used [$^{11}$C]RTI-32 PET, an *in vivo* marker of both dopamine and noradrenaline transporter binding, to localize differences between depressed and non-depressed patients. We studied eight and 12 Parkinson's disease patients with and without a history of depression matched for age, disease duration and doses of antiparkinsonian medication. The depressed Parkinson's disease cohort had lower [$^{11}$C]RTI-32 binding than non-depressed Parkinson's disease cases in the locus coeruleus and in several regions of the limbic system including the anterior cingulate cortex, the thalamus, the amygdala and the ventral striatum. Exploratory analyses revealed that the severity of anxiety in the Parkinson's disease patients was inversely correlated with the [$^{11}$C]RTI-32 binding in most of these regions and apathy was inversely correlated with [$^{11}$C]RTI-32 binding in the ventral striatum. These results suggest that depression and anxiety in Parkinson's disease might be associated with a specific loss of dopamine and noradrenaline innervation in the limbic system.**

**Keywords**: PET imaging; Parkinson's disease; depression; limbic system; catecholamines

**Abbreviations**: ADD = additional integrated image; BDI = Beck Depression Inventory; BP = binding potential; CingA = anterior cingulate cortex; DAT = dopamine transporter; NAT = noradrenaline transporter; ROI = region of interest; SPM = statistical parametric mapping; UPDRS = Unified Parkinson's Disease Rating Scale

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## Introduction

The frequency of depression in Parkinson's disease is ~40% (Brown and Jahanshahi, 1995; Cummings and Masterman, 1999). The rate of severe depression is twice that seen in other equivalently disabled patients (Rodin and Voshart, 1986). The natural history of depression in Parkinson's disease does not parallel the progression of physical symptoms, suggesting that it is an independent process that might affect vulnerable patients (Brown and Jahanshahi, 1995). However, the pathophysiology of depression in Parkinson's disease remains obscure. Some authors constructed models including multiple factors (Brown and Jahanshahi, 1995), whereas others postulate that neurochemical abnormalities may explain depression in Parkinson's disease (Cummings and Masterman, 1999). While widespread dopamine deficiency is the main feature of Parkinson's disease, other neurotransmitter systems degenerate or are altered by the degenerative process, such as the noradrenergic and serotoninergic brainstem nuclei (Halliday *et al*., 1990). Several studies have suggested the involvement of these neurotransmitters in the pathogenesis of depression in Parkinson's disease, but no clear pattern has emerged (Brown and Jahanshahi, 1995; Tom and Cummings, 1998).

We used [$^{11}$C]RTI-32 PET to study the role of catecholaminergic neurotransmission in the pathophysiology of depression in Parkinson's disease. [$^{11}$C]RTI-32 binds with similar nanomolar affinities to the dopamine (DAT) and

noradrenaline (NAT) membrane transporters but with far lower affinity to the serotonin transporter (Carroll *et al*., 1995). We compared the binding of this tracer in depressed and non-depressed Parkinson's disease patients who had similar age, disease severity and doses of antiparkinsonian medication.

## Subjects and methods

### *Subjects*

Twenty patients aged 58.5 ± 7.9 years were recruited from Movement Disorders clinics in London (Table 1). All fulfilled the UK PDS Brain Bank criteria for prospective diagnosis of idiopathic Parkinson's disease (Hughes *et al*., 1992). Disease duration ranged from 0.5 to 9.0 years and the Hoehn and Yahr stage was between 1 and 3.5. The patients were divided into two groups according to the presence ($n = 8$) or absence ($n = 12$) of episodes of major depression based on DSM-IV criteria. Parkinson's disease patients having a personal history of major depression that occurred before the beginning of Parkinson's disease or a Mini-Mental Parkinson score of <24 (Mahieux *et al*., 1995), were excluded. All subjects gave informed written consent and the study was approved by the Research Ethics Committees of the Imperial College School of Medicine (Hammersmith) and the Institute of Neurology. Permission to administer radiotracers was obtained from the Administration of Radioactive Substances Advisory Committee (UK).

All examinations took place while the depressed patients had been antidepressant free for at least 3 months. On the day of the PET study, neuropsychiatric evaluations were conducted on all patients. The Beck Depression Inventory (BDI) was used to quantify the severity of depression (Beck *et al*., 1961). Scores of apathy and anxiety were measured using the Apathy Evaluation Scale (Marin *et al*., 1991) and the State Trait Anxiety Inventory (Spielberger *et al*., 1970), respectively.

The depressed and non-depressed groups of Parkinson's disease patients were matched for age and disease severity measured using the Unified Parkinson's Disease Rating Scale (UPDRS)-3 score 'off' medication (Table 1). We also examined seven healthy subjects, age-matched to the patients (55.8 ± 13.6 years). None of these controls had any sign or history of neurological disorder or depression.

### *Image acquisition*

PET was performed with an ECAT966 HR++ tomograph (CTI-Siemens, Knoxville) with measured attenuation and scatter correction [resolution: 4 mm FWHM (full width at half-maximum)]. Patients withdrew all dopaminergic medication the day before the PET study to limit interactions between dopaminergic drugs and tracer uptake. An average of 222.7 ± 20.6 MBq of [$^{11}$C]RTI-32 with a specific radioactivity of 24 419.2 ± 6806.2 MBq/mmol was injected intravenously in the subjects and a 90 min acquisition in 3D mode was performed. Each subject underwent an MRI using a Picker 1 T system including a T1-weighted 3D volumetric acquisition to allow co-registration.

### *Image analysis*

The kinetics of [$^{11}$C]RTI-32 brain time activity curves were modelled using a simplified reference tissue compartmental approach to

**Table 1** *Parkinson's disease patient characteristics*

| Patient/sex | Age | Disease duration | UPDRS-3 | BDI | Apathy | Anxiety | L-Dopa eq. (mg) | Other medications |
|---|---|---|---|---|---|---|---|---|
| 1/M | 54 | 5.0 | 15.0 | 12 | 19 | 28 | 400.0 | |
| 2/F | 65 | 2.0 | 48.0 | 29 | 46 | 41 | 830.0 | |
| 3/M | 70 | 2.0 | 30.0 | 20 | 29 | 60 | 300.0 | |
| 4/F | 50 | 3.5 | 20.0 | 19 | 44 | 46 | 500.0 | |
| 5/M | 41 | 0.5 | 18.0 | 15 | 21 | 52 | 0 | |
| 6/M | 61 | 1.5 | 19.0 | 16 | 13 | 72 | 0 | |
| 7/M | 57 | 5.0 | 29.0 | 30 | 22 | 71 | 1780.0 | Cabergoline 5 mg, entacapone 600 mg |
| 8/F | 54 | 5.0 | 15.0 | 12 | 37 | 32 | 400.0 | |
| Mean | 56.5 | 3.1 | 24.3 | 19.1 | 18.8 | 50.3 | 526.3 | |
| (SD) | (9.0) | (1.8) | (11.2) | (7.0) | (7.3) | (16.6) | (573.4) | |
| 9/M | 67 | 3.0 | 29.5 | 7 | 10 | 37 | 400.0 | |
| 10/M | 64 | 8.0 | 28.0 | 4 | 5 | 21 | 610.0 | Entacapone 600 mg |
| 11/F | 61 | 6.0 | 14.0 | 3 | 8 | 32 | 300.0 | |
| 12/M | 57 | 4.0 | 15.0 | 6 | 12 | 51 | 300.0 | |
| 13/M | 68 | 2.0 | 22.0 | 3 | 9 | 30 | 350.0 | Cabergoline 3 mg |
| 14/F | 55 | 4.0 | 21.0 | 10 | 9 | 30 | 240.0 | |
| 15/M | 52 | 7.0 | 36.0 | 4 | 8 | 28 | 500.0 | |
| 16/M | 58 | 2.5 | 24.0 | 3 | 6 | 34 | 700.0 | Cabergoline 1 mg |
| 17/M | 58 | 9.0 | 26.5 | 9 | 10 | 27 | 350.0 | |
| 18/M | 70 | 8.0 | 26.0 | 3 | 25 | 27 | 1180.0 | Entacapone 800 mg |
| 19/F | 45 | 3.0 | 15.0 | 6 | 22 | 25 | 400.0 | |
| 20/M | 63 | 2.0 | 22.0 | 8 | 5 | 46 | 400.0 | |
| Mean | 59.8 | 4.9 | 23.3 | 5.5 | 5.2 | 32.3 | 477.5 | |
| (SD) | (7.2) | (2.6) | (6.7) | (2.5) | (2.7) | (8.7) | (257.8) | |

Patients 1–8 were those with and patients 12–20 those without episodes of major depression based on DSM-IV criteria. Disease duration is in years. L-Dopa eq. is the daily dose of all antiparkinsonian medication taken by the patient converted into L-Dopa equivalents (mg). When patients had drugs other than L-Dopa, these are listed in the last column. UPDRS-3 (motor) score was measured in patients 'off' medication. BDI = score given by the Beck Depression Inventory; apathy and anxiety were measured using the Apathy Evaluation Scale and the State Trait Anxiety Inventory, respectively (see Subjects and methods).

obtain a parametric image of the binding potential (BP) (Gunn *et al*., 1997). Radioactivity in the cerebellum was used as the non-specific tissue reference input (Guttman *et al*., 1997; Meyer *et al*., 2001). In addition, an integrated (ADD) image was created by summing the time series of [$^{11}$C]RTI-32 uptake scans collected 0–90 min after tracer administration.

We performed two image analyses, one using *a priori* placed regions of interest (ROIs) and the other using voxel-based statistical parametric mapping (SPM99, Wellcome Department of Cognitive Neurology, London).

### *ROIs*

The MRI of each subject was co-registred with the corresponding ADD image (Woods *et al*., 1993). ROIs were traced on each MRI and transferred onto the [$^{11}$C]RTI-32 BP image. The regions were: caudate, putamen, substantia nigra, thalamus, amygdala, anterior cingulate cortex (CingA, Brodmann areas 24–32), orbitofrontal cortex (OF, areas 11/47) and dorsolateral prefrontal cortex (DLPF, areas 10/45/46). These regions were chosen because they receive abundant monoaminergic projections or because of their implication in depression (Drevets, 1998; Mayberg *et al*., 1990; Ring *et al*., 1994).

### *SPM99 analysis*

The ADD image of each subject was transformed into standard stereotaxic space using a dedicated template. The BP images were transformed by applying the transformation parameters used for the corresponding ADD images. These normalized BP images were used for voxel-by-voxel comparisons.

### *Statistical analyses*

We compared clinical scores between depressed and non-depressed Parkinson's disease using the Student's unpaired *t* test. BP values obtained from the different ROIs in the controls, depressed and non-depressed Parkinson's disease patients were averaged over both hemispheres and compared using a two-way analysis of variance (ANOVA; Fisher's PLSD *post hoc* test). In addition, we performed an SPM99 voxel-by-voxel comparison between controls and all Parkinson's disease patients and between depressed and non-depressed Parkinson's disease patients. These comparisons were based on a two-tailed unpaired *t* test and *a priori* restricted to a volume of interest which included the striatum, the thalamus and amygdala in both hemispheres and the midbrain. This masking (small volume correction; Worsley *et al*., 1996) drastically reduces the number of voxel-by-voxel statistical comparisons, and a threshold of $P < 0.01$ (cluster-corrected at $P < 0.05$) was selected for considering statistical significance. Finally, we used SPM99 to explore the relationships between clinical scores of depression, apathy and anxiety and BP values in the Parkinson's disease patients ($n = 20$). A voxel-by-voxel correlation analysis between the individual scores and BP images was performed, this analysis being restricted to the volume mentioned above. These correlations were exploratory, with a statistical threshold for significance set at $P < 0.05$.

## Results

### *Clinical data*

There was no statistical difference between the depressed and non-depressed Parkinson's disease groups regarding age, disease duration, doses of anti-parkinsonian medication (L-Dopa equivalents) and UPDRS-3 'off' scores. The depressed cohort of patients had higher scores than the non-depressed patients for the BDI [$t(18) = 6.21$, $P < 0.0001$], apathy [$t(18) = 4.37$, $P = 0.0004$] and anxiety [$t(18) = 3.17$, $P = 0.005$].

### *PET: ROI analysis*

The ANOVA performed on BP values revealed a significant effect of both the group [controls, depressed Parkinson's disease and non-depressed Parkinson's disease, $F(2,26) = 18.6$, $P < 0.0001$] and the ROI [$F(9,26) = 409.1$, $P < 0.0001$] and an interaction between group and ROI ($F = 15.7$, $P < 0.0001$) (Table 2). *Post hoc* analyses showed that controls had higher BP values than both groups of Parkinson's disease patients in the caudate, putamen, ventral striatum and substantia nigra (Table 2). In addition, controls had higher values than depressed Parkinson's disease in the CingA and thalamus, and non-depressed Parkinson's disease had higher BP values than depressed Parkinson's disease in the thalamus, CingA, amygdala and locus coeruleus (Table 2).

**Table 2** *Results obtained with the regions of interest analysis*

| Region | Volume ($mm^3$) | Controls | Parkinson's disease depressed | Parkinson's disease non-depressed | *Post hoc* Fisher's PLSD | | |
|---|---|---|---|---|---|---|---|
| | | | | | Controls/ depressed | Controls/ non-depressed | Depressed/ non-depressed |
| Caudate | 3468 | 2.42 (0.47) | 1.65 (0.37) | 1.66 (0.39) | 0.001 | <0.001 | – |
| Putamen | 5744 | 2.79 (0.49) | 1.33 (0.22) | 1.49 (0.37) | <0.001 | <0.001 | – |
| Ventral striatum | 2040 | 2.05 (0.38) | 1.12 (0.37) | 1.37 (0.37) | <0.001 | <0.001 | – |
| SN | 1476 | 0.56 (0.11) | 0.29 (0.18) | 0.35 (0.21) | 0.006 | 0.02 | – |
| Midbrain | 1440 | 0.12 (0.07) | 0.09 (0.14) | 0.20 (0.12) | | | |
| Coeruleus | 512 | 0.22 (0.09) | 0.11 (0.16) | 0.24 (0.11) | | | 0.04 |
| Thalamus | 4492 | 0.46 (0.07) | 0.25 (0.17) | 0.37 (0.09) | 0.002 | – | 0.04 |
| Amygdala | 1696 | 0.26 (0.07) | 0.15 (0.18) | 0.28 (0.10) | | | 0.03 |
| CingA | 12 292 | 0.18 (0.07) | 0.01 (0.12) | 0.15 (0.10) | 0.002 | – | 0.005 |
| OF | 6596 | 0.02 (0.03) | –0.03 (0.12) | 0.07 (0.10) | | | |
| DLPF | 5876 | 0.05 (0.07) | 0.09 (0.16) | 0.06 (0.11) | | | |

SN = substantia nigra; OF = orbito-frontal cortex; DLPF = dorsolateral prefrontal cortex.

## *PET: SPM99 analysis*

### *Controls versus Parkinson's disease*

The controls had higher BP values than the whole Parkinson's disease group in the putamen, caudate, ventral striatum and substantia nigra, bilaterally (Fig. 1, Table 3).

### *Non-depressed versus depressed Parkinson's disease*

The non-depressed Parkinson's disease had significantly ($P < 0.01$, cluster-corrected at $P < 0.05$) higher BP values than depressed Parkinson's disease in the following regions: locus coeruleus bilaterally, mediodorsal thalamus bilaterally, inferior thalamus bilaterally, left ventral striatum and right amygdala (Fig. 2, Table 4).

### *Relationships between depression scores and BP values in Parkinson's disease patients*

We found a negative correlation between the BDI score and the BP in the left ventral striatum ($Z = 3.12$, $P = 0.001$, uncorrected, $x = -18$, $y = 10$, $z = 4$). The apathy score was negatively correlated with BP values in the ventral striatum, bilaterally (Table 5, Fig. 3). The anxiety score was negatively correlated with the BP values in the left ventral striatum, left caudate, left locus coeruleus, left inferior thalamic region, and bilaterally in the amygdala and medial thalamus (Table 6, Fig. 4).

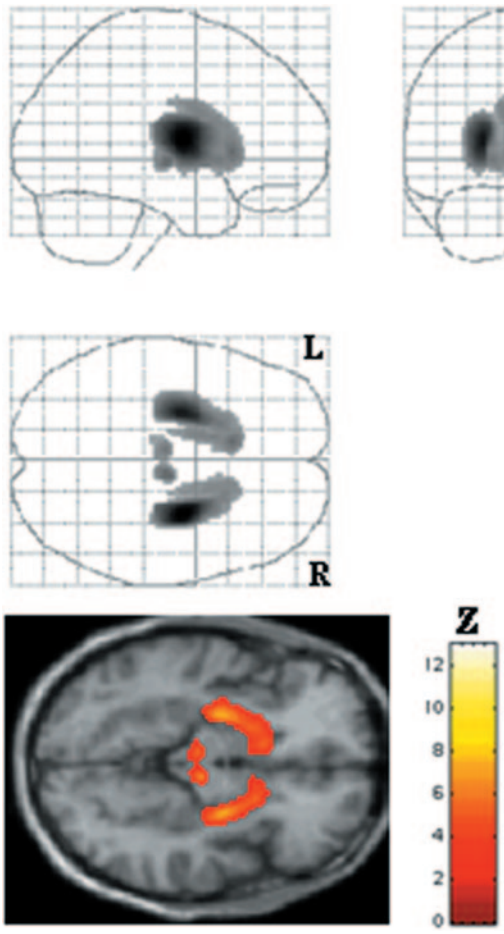


**Fig. 1** Regions with reduced [$^{11}$C] RTI-32 binding in the whole group of PD patients compared to controls ($P < 0.001$, corrected at ($P < 0.05$). Up: the glass view obtained with SPM99. Down: overlay on a MRI showing the loss of binding bilaterally in the striatum and susbtantia nigra of the patients.

**Table 3** *SPM99: controls versus Parkinson's disease patients*

| Region | Coordinates ($x$, $y$, $z$) | $Z$-score | Voxels ($n$) |
|---|---|---|---|
| Putamen R | 28, −6, 12 | 7.08 | 1104 |
| Putamen L | −26, −8, 10 | 6.56 | 1135 |
| Caudate R | 14, 12, 20 | 4.12 | 803 |
| Caudate L | −10, 20, 4 | 4.71 | 953 |
| Ventral striatum R | 20, 14, 0 | 4.37 | 100 |
| Ventral striatum L | −20, 12, 0 | 4.40 | 181 |
| Substantia nigra R | 8, −16, 0 | 6.30 | 107 |
| Substantia nigra L | −6, −16, 0 | 4.83 | 100 |

Regions where BP values are higher ($P < 0.001$, cluster-corrected at $P < 0.05$) in controls ($n = 7$) than in the Parkinson's disease patients ($n = 20$). R, L = right, left. The coordinates (in mm) refer to the Talairach and Tournoux atlas (1988). The last column indicates the cluster size (number of voxels in each statistical peak, with one voxel = 8 mm$^3$).

## Discussion

Depression in Parkinson's disease patients is associated with a reduction of [$^{11}$C]RTI-32 binding in several limbic regions. In addition, there is an inverse relationship between the binding of [$^{11}$C]RTI-32 in these regions and the severity of anxiety and mood disorders in these patients.

These abnormalities seem specific for depression in Parkinson's disease since we matched depressed and non-depressed Parkinson's disease patients for demography and locomotor disability, including age, disease duration, UPDRS-motor 'off' score and doses of antiparkinsonian medication. Accordingly, we found no difference between the two groups of patients for [$^{11}$C]RTI-32 uptake in the striatum or the substantia nigra.

Differences between depressed and non-depressed Parkinson's disease were observed using both an ROI analysis and voxel-based SPM. The slight differences between the results obtained using these approaches are explained by methodological considerations. For example, the CingA was not included in the masked SPM comparison in order to restrict the analysis to subcortical and brainstem areas and gain statistical power.

The decrease of [$^{11}$C]RTI-32 BP reflects a loss of catecholaminergic innervation in the corresponding regions of the brain. [$^{11}$C]RTI-32 binds mainly to DAT in the striatum (Carroll *et al*., 1995; Wilson *et al*., 1996), and the binding of this tracer is markedly reduced in the putamen of patients with Parkinson's disease (Guttman *et al*., 1997). We also found a reduction of [$^{11}$C]RTI-32 binding in the substantia nigra of Parkinson's disease patients. Thus, it is possible to demonstrate loss of dopaminergic cell function directly in the substantia nigra (Rakshi *et al*., 1999), since DAT is present on

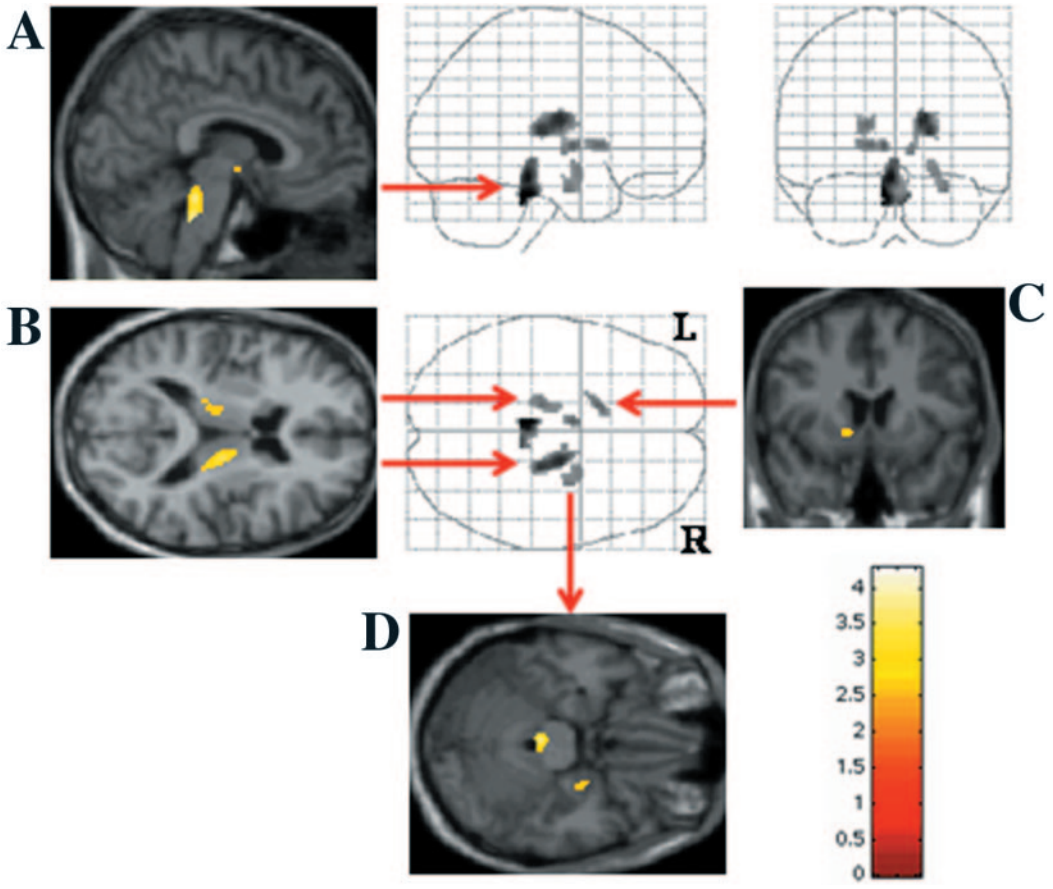


**Fig. 2** Regions where there is a significant reduction ($P < 0.01$) of [$^{11}$C]RTI-32 binding in the depressed compared to non-depressed PD patients. The regions seen in the glass view are shown overlayed on a MRI: (**A**) locus ceruleus; (**B**) medial thalamus; (**C**) left ventral striatum; (**D**) right amygdala.

**Table 4** *SPM99: non-depressed versus depressed Parkinson's disease*

| Region | Coordinates ($x$, $y$, $z$) | $Z$-score | Voxels ($n$) |
|---|---|---|---|
| Locus coeruleus L | −6, −32, −28 | 3.50 | 267 |
| Locus coeruleus R | 6, −34, −30 | 3.10 | 191 |
| Thalamus R | 16, −12, 16 | 3.10 | 532 |
| Thalamus L | −16, −22, 14 | 2.68 | 454 |
| Ventral striatum L | −16, 10, 2 | 2.68 | 480 |
| Amygdala R | 30, −6, −24 | 2.60 | 229 |

Regions where BP values are higher ($P < 0.005$, corrected at $P < 0.05$ at the cluster level) in non-depressed ($n = 12$) than in depressed ($n = 8$) Parkinson's disease patients. R, L = right, left. The coordinates (in mm) refer to the Talairach and Tournoux atlas (1988).

**Table 5** *Regions in which BP is negatively correlated with apathy*

| Region | Coordinates ($x$, y, $z$) | $Z$-score | $P$-value | Voxels ($n$) |
|---|---|---|---|---|
| Ventral striatum L | −20, 6, 4 | 2.37 | 0.009 | 96 |
| Ventral striatum R | 16, 14, 0 | 2.02 | 0.022 | 50 |

Exploratory analysis with $P < 0.05$, uncorrected. R, L = right, left. The coordinates (in mm) refer to the Talairach and Tournoux atlas (1988).

the dendrites of dopaminergic neurons (Nirenberg *et al*., 1996).

[$^{11}$C]RTI-32 has nanomolar affinity for the NAT, whereas it has a low affinity for the serotonin transporter (Carroll *et al*., 1995). Therefore, part of the decrease of [$^{11}$C]RTI-32 binding observed in depressed Parkinson's disease patients could be related to loss of noradrenergic terminals. This is supported by the finding that [$^{11}$C]RTI-32 binding was reduced in the locus coeruleus and in the thalamus. In addition, the locus coeruleus sends noradrenergic projections to the frontal cortex, the amygdala and the ventral striatum (Ressler and Nemeroff, 1999). Altogether, this suggests that the decrease of [$^{11}$C]RTI-32 binding observed in the depressed Parkinson's disease patients corresponds to the loss of both dopamine and noradrenaline projections. Alternatively, the downregulation of DAT and NAT binding might be secondary to reduced release of endogenous ligand in these synapses (Metzger *et al*., 2002). Nevertheless, in Parkinson's disease patients, we suspect that loss of catecholaminergic terminals (Paulus and Jellinger, 1991) plays a much more dominant role in the reduction of [$^{11}$C]RTI-32 binding observed in this study than any

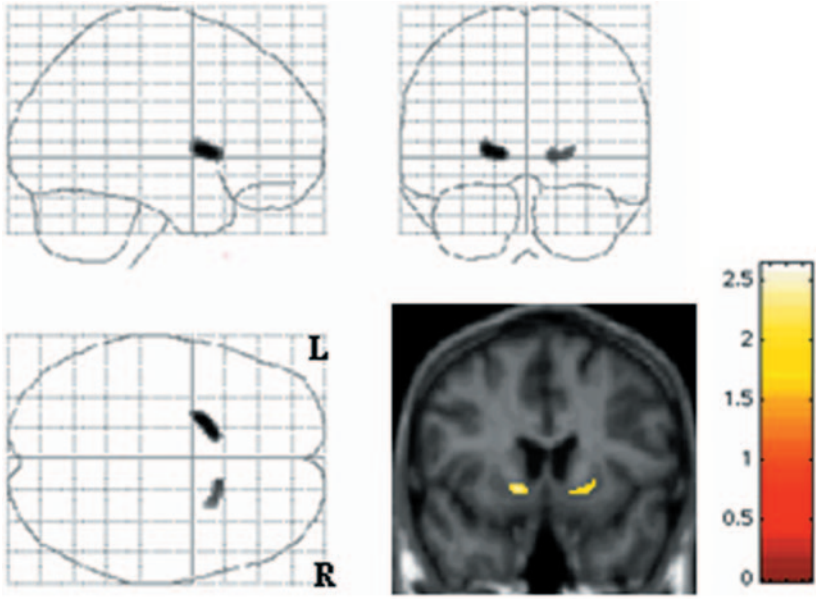


**Fig. 3** The [$^{11}$C]RTI-32 binding in the ventral striatum is inversely correlated ($P < 0.05$) with apathy in the whole group of patients.

**Table 6** *Regions in which BP is negatively correlated with anxiety*

| Region | Coordinates (*x*, *y*, *z*) | *Z*-score | *P*-value | Voxels (*n*) |
|---|---|---|---|---|
| Ventral striatum L | −18, 10, 8 | 2.72 | 0.003 | 292 |
| Caudate L | −12, 14, 14 | 2.34 | 0.010 | 55 |
| Locus coeruleus L | −6, −30, −18 | 2.70 | 0.003 | 131 |
| Thalamus R | 16, −10, 16 | 2.55 | 0.005 | 365 |
| Thalamus L | −6, −8, 12 | 2.38 | 0.009 | 292 |
| Amygdala R | −22, 0, −10 | 2.10 | 0.018 | 34 |
| Amygdala L | −24, 4, −14 | 2.06 | 0.020 | 47 |

See footnotes of Table 5.

pharmacodynamic regulation of the transporter density on the remaining membranes.

Dopamine interactions with the limbic system are probably involved in stress and depression (Cabib and Puglisi-Allegra, 1996). In Parkinson's disease, pessimism measured using the harm-avoidance personality score was reported to be correlated with [$^{18}$F]Dopa uptake in the right caudate nucleus (Kaasinen *et al*., 2001). Mood fluctuations can occur independently from motor fluctuations (Maricle *et al*., 1995), implicating involvement of ventral rather than dorsal brain circuitary, and are often improved by antiparkinsonian medication (Czernecki *et al*., 2002). Parkinsonian patients with major depression do not feel euphoria following administration of the dopamine-releasing agent methylphenidate. This has been attributed to degeneration of the dopaminergic innervation of the limbic system (Cantello *et al*., 1989).

The role of noradrenaline in affective disorders is widely documented (Ressler and Nemeroff, 1999; Sullivan *et al*., 1999). A loss of pigmented neurons has been found in the locus coeruleus of suicide victims (Arango *et al*., 1996), and the level of NAT is reduced post-mortem in the locus coeruleus of patients with major depression (Klimek *et al*., 1997). The degeneration of the locus coeruleus occurring in Parkinson's disease (Paulus and Jellinger, 1991) might play a role in mood changes in these patients (Zweig *et al*., 1993). This is supported here by the lower [$^{11}$C]RTI-32 binding found in the locus coeruleus of depressed compared with non-depressed patients. In addition, the negative correlation found between locus coeruleus [$^{11}$C]RTI-32 binding and severity of anxiety in Parkinson's disease supports a direct role for noradrenaline in the pathophysiology of anxiety in Parkinson's disease.

It is striking that the reduction of catecholaminergic innervation in depressed Parkinson's disease patients occurs in regions thought to comprise the emotional circuits of the brain. Indeed, the amygdala, mediodorsal thalamus, ventral striatum and CingA belong to the limbic system and have been implicated as dysfunctional regions in mood disorders (Drevets, 1998).

The amygdala is a key structure for emotional processing in humans (LeDoux, 2000). Functional abnormalities in the amygdala correlate with severity of endogenous depression (Drevets, 1998), and the amygdala mediates fear processing and anxiety (LeDoux, 2000). The amygdala connects with locus coeruleus and receives a noradrenergic and dopaminergic innervation (Fallon *et al*., 1978; Fudge and Emiliano, 2003) which is reduced in Parkinson's disease (Moore, 2003). In addition, it has been reported in a post-mortem study that Parkinson's disease patients have up to a 20% reduction of amygdala volume and that this structure contains Lewy bodies (Harding *et al*., 2002). In our study, [$^{11}$C]RTI-32 binding was significantly reduced in the right amygdala of depressed Parkinson's disease patients and the anxiety score was negatively correlated with bilateral amygdala [$^{11}$C]RTI-32 binding. The loss of noradrenaline and dopamine in the

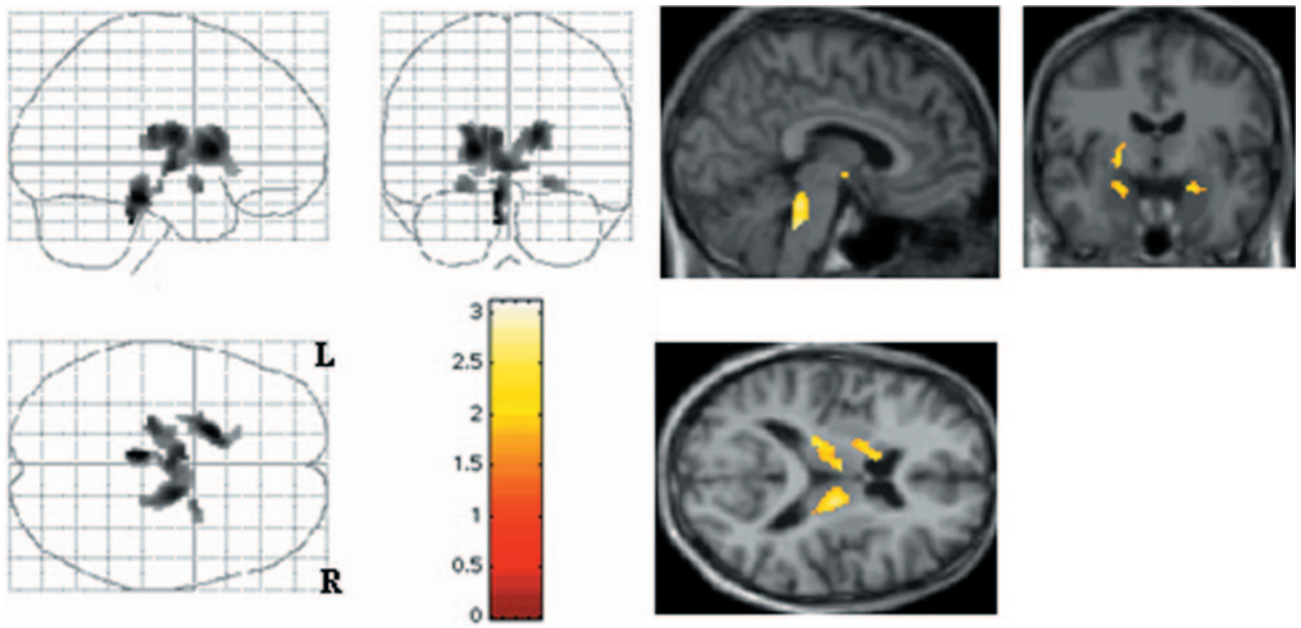


**Fig. 4** Regions in which anxiety is inversely correlated ($P < 0.05$) with [$^{11}$C]RTI-32 binding. Left: SPM99 glassview. Right: overlay on a MRI showing the locus ceruleus (sagittal view), the left ventral striatum and left and right amygdala (coronal view) and the medial thalamus bilaterally and left ventral striatum (axial view).

amygdala is likely to play a role in generating affective symptoms in Parkinson's disease.

The amygdala has connections with the CingA (LeDoux, 2000) where, with an ROI analysis, we found a reduction of [$^{11}$C]RTI-32 binding in the depressed compared with the non-depressed Parkinson's disease patients. The CingA is part of the limbic system and involved in many cognitive and emotional processes (Paus *et al*., 1993; Drevets, 1998). In addition, the CingA receives a strong dopaminergic and noradrenergic innervation (Williams and Goldman-Rakic, 1993). Two PET studies have revealed CingA hypometabolism associated with depression in Parkinson's disease (Ring *et al*., 1994; Mentis *et al*., 2002). Our results suggest that such dysfunction of CingA in depressed Parkinson's disease might be related to a specific loss of catecholaminergic projections.

Noradrenergic projections to the thalamus target the medial and intralaminar subnuclei (Oke *et al*., 1997), where we found a significant loss of [$^{11}$C]RTI-32 binding in depressed compared with non-depressed Parkinson's disease patients. The role of the thalamus in depression is unclear. However, a recent study showed that depression and anxiety induced by α-methylparatyrosine, a tyrosine hydroxylase inhibitor, was associated with a marked reduction of glucose metabolism in the thalamus (Bremner *et al*., 2003). The role of the thalamus in affective disorders might be related to its involvement in arousal. Indeed, anxiety is associated with changes in vigilance that implicate the same thalamo-cortical interactions which are under the control of the noradrenergic innervation originating in the locus coeruleus (Ressler and Nemeroff, 1999; David Johnson, 2003). Accordingly, the correlation between anxiety and [$^{11}$C]RTI-32 binding in the thalamus in these patients suggests that impaired noradrenergic modulation of thalamic activity plays a role in the generation of anxiety in Parkinson's disease.

Finally, depressed Parkinson's disease patients showed a relative reduction of [$^{11}$C]RTI-32 binding in the ventral striatum, which is involved in emotional processing via its connections with frontal limbic regions (Nakano, 2000). The dopaminergic system is less affected in the ventral striatum than more dorsal regions in Parkinson's disease (Kish *et al*., 1988), but receives most of the noradrenergic afferents of the striatum (Nicola and Malenka, 1998). In non-parkinsonian depressed patients, a single photon emission computed tomography (SPECT) study using [$^{123}$I]β-CIT reported an increase of tracer uptake in the striatum compared with controls (Laasonen-Balk *et al*., 1999). However, [$^{123}$I]β-CIT also binds to the serotonin transporter (Carroll *et al*., 1995) and increased uptake may reflect serotonin transporter upregulation in depression. Conversely, a recent study reported a decrease of [$^{11}$C]RTI-32 binding in the ventral striatum of depressed subjects (Meyer *et al*., 2001). In line with this result, we found a reduction of the [$^{11}$C]RTI-32 binding in the left ventral striatum of the depressed Parkinson's disease patients. Interestingly, we found that [$^{11}$C]RTI-32 binding in the ventral striatum was inversely correlated with the degree of apathy and the intensity of depression in the patients. It seems that the dopaminergic and noradrenergic innervation of the ventral striatum is involved in both endogenous and Parkinson's disease depression, and, might specifically play a role in apathy which is a major feature of depression. Interestingly, L-Dopa treatment might improve motivation in some patients with Parkinson's disease (Czernecki *et al*., 2002).

In conclusion, our results suggest that depression in Parkinson's disease is associated with a specific loss of

dopamine and noradrenaline innervation of cortical and subcortical components of the limbic system. These results might help in understanding the functional anatomy of depression in Parkinson's disease and have therapeutic implications.

These results might be replaced in the more general context of the relationships between ageing, depression and catecholamines. Briefly, the reduction of catecholaminergic innervation that occurs in the cortical limbic structures might participate in the loss of cognitive abilities such as flexibility, attention or executive functions that is known to occur with ageing (Nieoullon, 2002). On the same lines, it is considered that increased anxiety found in elderly people might be related to the loss of dopaminergic and noradrenergic innervation, especially in the amygdala (Gareri *et al*., 2002). Therefore, some authors have suggested that pre-depressive and pre-dementia states that are sometimes observed with ageing have underlying pathophysiology in common with Parkinson's disease (Gareri *et al*., 2002).

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