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Levodopa Challenge Neuroimaging of Levodopa-Related Mood Fluctuations in Parkinson's Disease

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Some patients with advanced Parkinson's disease (PD) develop dose-related fluctuations in mood. This may reflect alterations in dopamine-influenced brain circuits that mediate emotion. However, there is no available information to localize which dopamine-influenced neurons may be most affected. Eight patients with PD and clinically significant levodopa-related mood fluctuations (mania, depression, or anxiety) were compared to 13 patients with similarly severe PD and fluctuations of motor function but not of mood. Regional cerebral blood flow (rCBF) was measured with positron emission tomography before and after levodopa (in the presence of carbidopa). The rCBF response to levodopa in medial frontal gyrus and posterior cingulate cortex (PCC) significantly differed between mood fluctuators and control patients (corrected $p<0.02$). Other regions with uncorrected $p<0.001$ in this comparison were cortical Brodmann areas 22, 40, 13, 11, and 28, hippocampus, and claustrum. The levodopa activation paradigm detected group differences not evident in a comparison of resting rCBF. Abnormalities of dopamine innervation may produce mood fluctuations via effects on PCC, an area strongly linked to mood and anxiety and with known rCBF responsiveness to levodopa or D2-like dopamine receptor agonists. We speculate that mood fluctuations may arise in parkinsonian patients who have abnormal dopaminergic modulation of caudate nucleus, anterior cingulate cortex, or orbital frontal cortex, all of which innervate PCC. The findings require confirmation in larger and better-matched groups.

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INTRODUCTION

'I find my 'offs' are accompanied by a curiously deep and malevolent depression.'
from a patient with Parkinson's disease (Lees, 1989)

Mood and anxiety disorders comprise major public health problems. When mood symptoms arise in relation to specific anatomic or pharmacologic insults, this relationship may lead to knowledge of how mood symptoms are produced. One such experiment of nature occurs in some patients with advanced Parkinson's disease (PD).

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Loss of dopamine-producing cells in the midbrain produces the symptoms of PD (Hornykiewicz, 1963). Levodopa (L-dihydroxyphenylalanine, L-DOPA) is a natural precursor of dopamine that crosses the blood–brain barrier and is widely used to treat PD. Early in the disease course, levodopa commonly produces dramatic and sustained symptomatic relief (Cotzias *et al*, 1967). However, later in the course of the illness, the benefit from a dose of levodopa may wane soon after it appears; this is referred to as 'end-of-dose deterioration' or 'wearing off.' Commonly patients and physicians refer to 'on' periods, when the medication is providing motor benefit, and 'off' periods, when the parkinsonian symptoms return. Interestingly, this nomenclature derives from a patient 'who likened the glow of the levodopa awakening to the switching on of a light and the equally abrupt return of parkinsonian darkness to the light going off' (Lees, 1989; Duvoisin, 1974).

As this poetic description suggests, the motor fluctuations that define the on and off states are often accompanied by fluctuations of nonmotor CNS symptoms, including pain, autonomic dysfunction, cognitive problems, or emotional

changes. Some sadness with increased disability is not surprising, and mild mood fluctuations occur in almost all PD patients with motor fluctuations (Nissenbaum *et al*, 1987; Hardie *et al*, 1984; Menza *et al*, 1990; Maricle *et al*, 1995a, b). These fluctuations are not always tightly correlated to levodopa dosing (Menza *et al*, 1990; Richard *et al*, 2001). However, a minority of patients develop severe depression, anxiety, or mania, usually with a more predictable relationship to levodopa dosing (Damásio *et al*, 1971; Hardie *et al*, 1984; Keshavan *et al*, 1986; Nissenbaum *et al*, 1987; Lees, 1989; Friedenberg and Cummings, 1989; Menza *et al*, 1990; Goodwin, 1990; Riley and Lang, 1993; Vázquez *et al*, 1993; Siemers *et al*, 1993; Maricle *et al*, 1995a, b). The focus of this report is on these more clinically significant symptoms, usually called 'mood fluctuations' in the PD literature.

These symptoms are no mere academic curiosity. Patients consider mood symptoms more disabling than their motor deficits, and caregivers consider them more stressful (Witjas *et al*, 2002; Carter *et al*, 2002). Patients with clinically significant mood fluctuations tend to have severe PD, with early onset, long duration of illness, and extremely high rates of psychiatric comorbidity including dementia, prior (nonfluctuating) depression, and drug-induced psychosis (Racette *et al*, 2002).

There is some evidence that fluctuations of mood or anxiety in PD result from a direct effect of levodopa on selected brain pathways rather than a secondary psychological response to fluctuating disability. Supporting this view, mood response to a dose of levodopa precedes the improvement in motor function (Maricle *et al*, 1995a). Under blind conditions, a placebo causes no similar mood effect (Maricle *et al*, 1995b). The extent of mood change does not correlate tightly with the extent of motor improvement or with baseline severity of motor signs (Maricle *et al*, 1995a, 1998; Witjas *et al*, 2002). Finally, patients with rheumatoid arthritis and similar fluctuations in motor disability have significantly less severe fluctuations of mood (Cantello *et al*, 1986).

These observations suggest that PD patients with levodopa-related emotional fluctuations may have dysfunction of dopaminergic afferents to brain regions that mediate emotional responses. Unfortunately, existing data are insufficient to clarify the pharmacology or functional neuroanatomy of this fascinating dopamine-related mood syndrome.

We used an extensively validated pharmacologic challenge neuroimaging technique to identify brain structures that may be involved in the experience or provocation of emotion. Specifically, we compared regional cerebral blood flow (rCBF) responses to levodopa in PD patients with clinically significant mood fluctuations to responses in patients with similarly severe PD and motor fluctuations but no mood fluctuations. Regional CBF responses to levodopa challenge are well characterized in normal and parkinsonian humans and in other primates (Hershey *et al*, 1998, 2000, 2003). Pretreatment with carbidopa blocks dopamine production outside the brain and consequently prevents indiscriminate vascular effects (Hershey *et al*, 1998, 2000, 2003; Black *et al*, 2003). We hypothesized that mood fluctuators would show regional abnormalities in the rCBF response to levodopa, compared to similarly ill PD controls, reflecting altered dopamine-mediated neuronal function in specific neuroanatomical circuits that affect emotion.

METHODS

Clinical Methods

The Radioactive Drug Research Committee and the Human Studies Committee of Washington University School of Medicine (WUSM) approved this research, and all participants gave informed consent to participation. Over a 5-year period, patients with clinically diagnosed idiopathic PD were recruited from the WUSM Movement Disorders Center and through the American Parkinson Disease Association. All subjects underwent extensive psychiatric and neurological evaluation by a movement disorders specialist who is board certified in psychiatry and geriatric psychiatry. In addition, symptom severity at baseline was rated using the Mini-Mental Status Exam, Hamilton Depression Rating Scale, Hamilton Anxiety Scale, Bech mania scale, Unified Parkinson Disease Rating Scale (UPDRS), and Barnes akathisia scale.

These scales are neither practical nor most appropriate for repeated ratings of symptom severity while the patient was in the positron emission tomography (PET) scanner. Instead, patients rated various symptoms using the visual analog scale (VAS) (Folstein and Luria, 1973). The VAS ratings were recorded on 100 mm anchored scales and included sad–happy, akathisia, calm–anxious, pain, tremor, 'slowness and stiffness,' dystonia, dyskinesias, disability–independence, and apathy–motivation. All patients practiced the VAS ratings prior to the first scan and definitions were clarified with each scan using written guidelines and appropriate follow-up.

All 21 subjects had motor fluctuations as defined by a history of marked fluctuations in motor symptoms in response to individual doses of PD medications, in spite of appropriate pharmacological adjustments. There is no accepted convention for diagnosis of mood fluctuations. We used the criteria listed in Appendix A1 to diagnose 'clinically significant levodopa-related mood fluctuations' in eight patients and to exclude this diagnosis in 13 patients ('motor fluctuator controls'). Dose-related depressive, anxious, or manic symptoms were all included in the mood fluctuation group, since most such patients have both depressive and anxious symptoms when off, and some have on-period mania and off-period anxiety (Racette *et al*, 2002). Appendix A1 also contains dialogue from a representative screening interview in one patient.

All patients were excluded for other neurological illness, other psychiatric illness (except remitted major depression), or concurrent systemic illness likely to affect the CNS or make study participation unsafe. Demographic and diagnostic information is provided in Table 1.

Protocol

Patients abstained from food and antiparkinsonian medication for at least 8 h prior to the study. (A longer interruption in treatment was not feasible given the marked severity of motor disability when 'off' in several patients.) They took 200 mg carbidopa by mouth and baseline ratings of severity

Table 1 Demographic and Illness Information

	Mood fluctuators	Motor fluctuator controls
Number	8[a]	13
Age	59±10	61±8
Sex (F)	6	5
Handedness (RH)	7	10
Years PD	12±6	10±3
Severity (H&Y)[b]	2.2±0.3	2.5±0.7
Worst side (R>L)	2	3
Antidepressant[c]	6	5
Usual daily antiparkinsonian dose (mg)[d]	1217±380	862±338*

[a]See Table 5 for specific mood fluctuation types.
[b]H&Y: Hoehn and Yahr scale.
[c]Currently taking an antidepressant at any dose. In mood fluctuators these were: sertraline in three subjects (25, 150, and 150 mg/day); mirtazapine in two subjects (15 and 60 mg/day); amitriptyline in one subject (25 mg/day). Each of the following regimens was used by one motor fluctuator control: venlafaxine (225 mg/day) and trazodone (50 mg/day); paroxetine (20 mg/day) and imipramine (50 mg/day); sertraline 100 mg/day; trazodone (175 mg/day); amitriptyline (50 mg/day).
[d]Equivalent dose of levodopa or dopamine agonists using the method of Hobson *et al* (2002). Other medications included amantadine (one mood, three motor), selegiline (zero mood, two motor), and benztropine (zero mood, one motor).
*$p<0.05$, uncorrected for multiple comparisons (all other table rows $p>0.10$).

were recorded. Subjects then were placed in the scanner with an individually molded polyform mask to help minimize head movement. A 20-gauge catheter was inserted into an antecubital vein to permit injection of $H_2^{15}O$.

We performed three baseline PET measurements of rCBF at least 10 min apart. We then administered levodopa and repeated three PET rCBF scans. During each PET scan, the room was darkened and quiet, and subjects remained still with eyes closed. Just before or after each scan (when possible), patients recorded VAS symptom ratings and we performed modified UPDRS ratings. We selected items from motor subscale 3 from UPDRS that could be assessed with the patient in the scanner, including tremor, rigidity, and bradykinesia for upper extremities (16 total possible points for each side, 32 points total) (Hershey *et al*, 1998). Initially, levodopa was administered orally as 150 mg levodopa/37.5 mg carbidopa, but after difficulties with variable absorption in some patients in a parallel study we abandoned this in favor of an approximately bioequivalent dose given by the intravenous (i.v.) route (the intermediate-dose protocol in Black *et al*, 2003). By way of comparison, the average usual morning dose of antiparkinsonian medication in these patients was equivalent to about 250 mg levodopa using the formula of Hobson *et al* (2002), with no group difference (*t*-test, $p>0.30$). Seven subjects in each group received levodopa i.v. The on-levodopa scans were performed at ~45–75 min after oral levodopa or ~30–60 min after the start of the i.v. infusion; these times were chosen *a priori* to match the expected time of peak blood levels (for oral dosing) and to approximate these same blood levels (for i.v. dosing).

Levodopa/Carbidopa Quantification

In patients who received oral levodopa, blood samples for determination of plasma levodopa concentration were taken through the i.v. catheter. In patients who received i.v. levodopa, the sampling was performed through a second 20-gauge catheter placed in a vein in the contralateral upper extremity. Samples were taken before administration of levodopa and again just after each post-levodopa PET scan. Concentrations were measured using high-performance liquid chromatography with electrochemical detection (Baruzzi *et al*, 1986; Carl and Perlmutter, 1998).

PET Methods

PET studies were performed in 2D mode on a Siemens 953B or 961 HR scanner (CTI, Knoxville, TN). Only one subject in each patient group was studied on the 953B scanner. On the 953B scanner, data were recorded simultaneously for 31 slices with a center-to-center slice separation of 3.4 mm. On the 961 scanner, data were recorded simultaneously for 47 slices with a 3.25 mm center-to-center slice separation. After subjects were positioned, a transmission scan used for individual attenuation correction was acquired with rotating rod sources containing $^{68}Ge/^{68}Ga$. Blood flow was measured using a 40-s emission scan following the i.v. bolus injection of 5–10 ml of saline containing 40–50 mCi of ^{15}O-labeled water (Raichle *et al*, 1983; Herscovitch *et al*, 1983; Videen *et al*, 1987).

Image Processing

Data from both scanners were combined, given the similar image resolution and the limited number of available subjects. Images were aligned within subject and non-linearly transformed to match the MNI instantiation of Talairach and Tournoux atlas space, using the methods in the SPM99 software package (http://www.fil.ion.ucl.ac.uk/spm/spm99.html) (Talairach and Tournoux, 1988; Mazziotta *et al*, 1995; Friston *et al*, 1995). The atlas-transformed images were spatially filtered with an 18 mm (FWHM) Gaussian filter and intensity normalized.

Statistical Analysis

Clinical features were compared using a two-tailed *t*-test for quantitative data and the χ^2-test for categorical data. Changes with levodopa were tested using repeated measures ANOVA.

Only voxels present in all atlas-transformed images were further analyzed. (The most superior part of cortex was not covered in the two 953b subjects.) Using SPM99, a general linear model was computed at each voxel with variables coding for diagnosis (mood fluctuations *vs* motor fluctuations only), drug status (baseline *vs* on-levodopa), and individual (a Boolean variable for each subject). The primary contrast compared response to levodopa between the two patient groups. Fixed effects analysis was performed given the small numbers of subjects in each group. Secondary analyses were (1) a between-group comparison of baseline rCBF and (2) the response to levodopa across all subjects. Using SPM99, the statistical significance was

corrected for multiple comparisons based on the size of each cluster of contiguous voxels having $t > 3.17$, corresponding to $p = 0.001$ uncorrected (df = 100). The *a priori* decision was to consider significant only clusters with a corrected $p < 0.05$. However, this is a conservative choice and may not detect all meaningful responses. Therefore, we also report all other intracerebral clusters defined by voxelwise $p < 0.001$. We also report an experimentwise (also called 'omnibus' or 'set-level') statistic reflecting the likelihood, computed by SPM99, of obtaining by chance the observed number of suprathreshold clusters.

Relative CBF in regions identified by the statistical analysis was further examined as follows. Spherical volumes of interest (VOIs) with diameter 8 mm were centered on local maxima at least 8 mm apart ('peaks'), and average voxel values from each VOI were obtained from each atlas-transformed, smoothed rCBF image and expressed as the ratio to the average voxel value in all analyzed voxels.

RESULTS

PET: Comparison of Baseline rCBF between Mood Fluctuators and Controls

There were no statistically significant responses at corrected $p < 0.05$. At an uncorrected threshold corresponding to $p < 0.001$, one small cluster of voxels, with local maximum (peak) at (−2,−54,20), showed lower baseline rCBF in the mood fluctuator group (peak $t = 3.76$, 19 df, 0.2 ml). This peak lies in the posterior cingulate cortex (PCC) (Brodmann area (BA) 23) near retrosplenial cortex, 32 mm posterior and inferior to the PCC peak from the levodopa challenge analysis.

PET: Levodopa Response across All Subjects

Responses to levodopa across both groups included significant regional increases in blood flow (experimentwise $p < 0.0002$), with the largest cluster encompassing midbrain and pons and extending into temporal lobe and thalamus (see Table 2; uncorrected $p \ll 10^{-5}$; 73.5 ml). Regional CBF also increased significantly in three other clusters, including lateral orbital cortex, bilateral insula, and middle and superior frontal gyrus (see Table 2). In the opposite direction, there was a significant pattern of decreased rCBF after levodopa (experimentwise $p \ll 10^{-5}$), but there were no clusters with peaks in the brain for which corrected $p < 0.05$. At the uncorrected threshold of $t > 3.17$, levodopa decreased rCBF in two small intracerebral clusters, one in cerebellum (peak $t = 3.54$ at (18,−62,−20), 0.5 ml) and in medial motor cortex (BA4; peak $t = 3.45$ at (−2,−36,58), 0.3 ml).

PET: Comparison of Response to Levodopa between Mood Fluctuators and Controls

There was a significant difference between groups in the regional blood flow response to levodopa (mood > nonmood, experimentwise $p = 0.002$; mood < nonmood, experimentwise $p < 10^{-5}$). One cluster of voxels centered in the brain met the predetermined criterion for significance after correction for multiple comparisons. This cluster was identified in the mood > nonmood comparison (corrected $p < 0.01$) and contained two peaks centered at (−2,−26,54) and (−6,−26,36) (see Table 3 and Figure 1, top row). The first peak in this region is centered in medial frontal gyrus near the central sulcus, and the second peak lies in PCC. Mean values from spherical VOIs centered on these peaks show that PD control patients have decreased rCBF after levodopa, while mood fluctuators do not (repeated measures ANOVA, $F_{1,19} = 5.086$, $p < 0.04$; *post hoc* Scheffe tests indicate a decrease with levodopa in the motor fluctuator group at $p < 0.06$ but $p > 0.25$ for all other comparisons). Data from the PCC peak are summarized in Figure 2. Other voxel clusters exceeding $t = 3.17$ are described in Table 3 and Figure 1.

No intracerebral cluster in the mood < nonmood comparison reached the specified significance criterion, but one cluster with corrected $p < 0.08$ had peak $t = 4.37$ at (20,−22,−16) in the body of the hippocampus (2.6 ml). The only other intracerebral voxel clusters surpassing

Table 2 Most Significant Regional Effects of Levodopa across All Subjects

Cluster *p*(cor)	No. of voxels	Voxel's *t*	*x,y,z* (mm)	Description	BA
$\ll 10^{-5}$	9187	9.69	−4,−30,−26	Pons	—
		4.56	−24,−16,−12	Parahippocampal gyrus	28
		4.00	−24,−10,−38	Parahippocampal gyrus/uncus	36/20
		3.52	18,−26,16	Thalamus (pulvinar)	—
0.002	949	6.47	36,42,−14	Middle frontal gyrus	11
0.001	1032	5.97	−42,−28,18	Insula	13
		4.91	−32,−32,30	WM deep to inf. parietal lobule	—
$< 10^{-5}$	2179	5.58	48,10,30	Middle frontal gyrus	9
		4.45	26,22,36	WM deep to BA9	—
		3.69	14,50,28	Superior frontal gyrus	9
0.089	304	4.38	−24,28,−20	Inferior frontal gyrus	11
0.082	316	4.29	50,−30,26	WM deep to inf. par. lobule	40

Most significant clusters of contiguous voxels with $t > 3.17$ (100 df), and local maxima within each cluster separated by more than 8 mm. See legend to Table 2 for abbreviations.

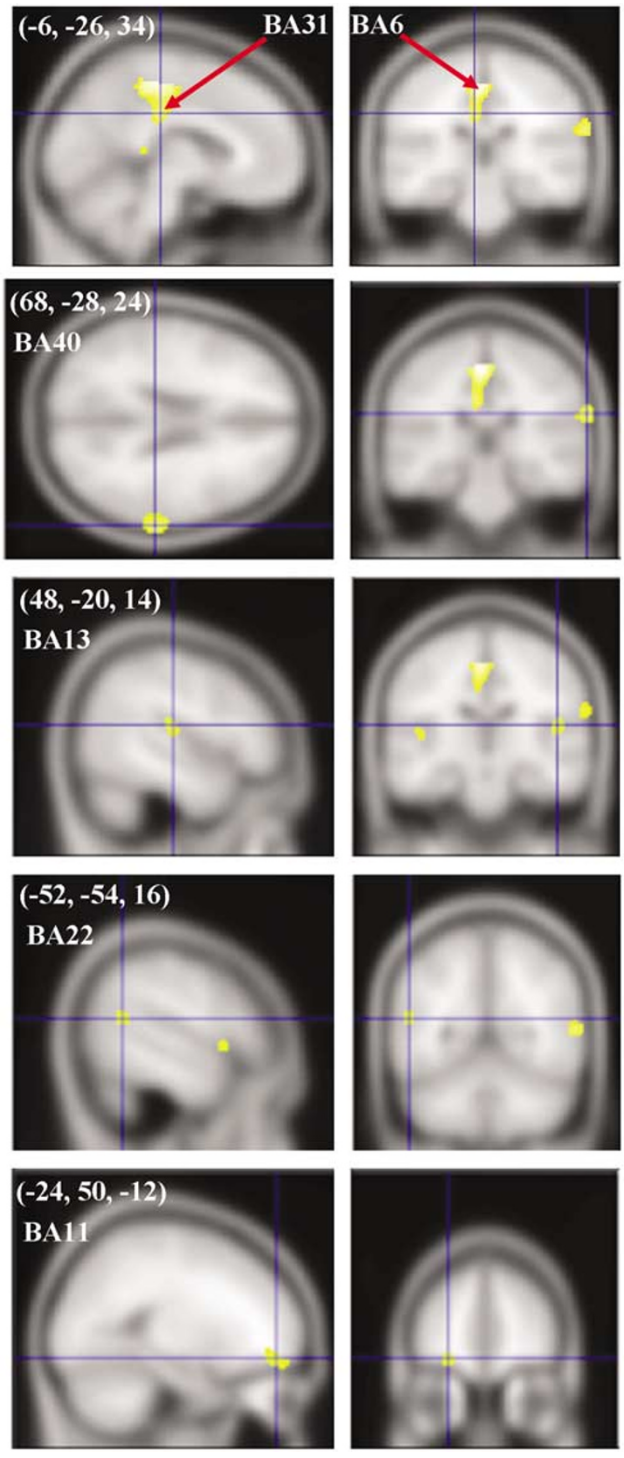

Figure 1 Top row: Mood fluctuators differed significantly from control patients with motor fluctuations only (Table 2). The t image is shown in color superimposed on an averaged structural MR image in grayscale. The crosshairs are at the statistical peak in PCC (−6,−26,34). On coronal images, the right side of the brain is shown on the right side of the figure. Other rows: Additional regions of possible group difference in levodopa response (Table 2). From top to bottom: Inferior parietal lobule, crosshairs at (68,−28,24), insula (48,−20,14), superior temporal gyrus (−52,−54,16), lateral orbital cortex (−24,50,−12).

$t = 3.17$ had peaks at (28,4,−20) (uncus, BA28, peak $t = 4.01$, 1.1 ml), (−26,−22,18) (claustrum, peak $t = 3.69$, 0.3 ml), and (−24,−2,−40) (uncus, near BA20, peak $t = 4.01$, 0.2 ml).

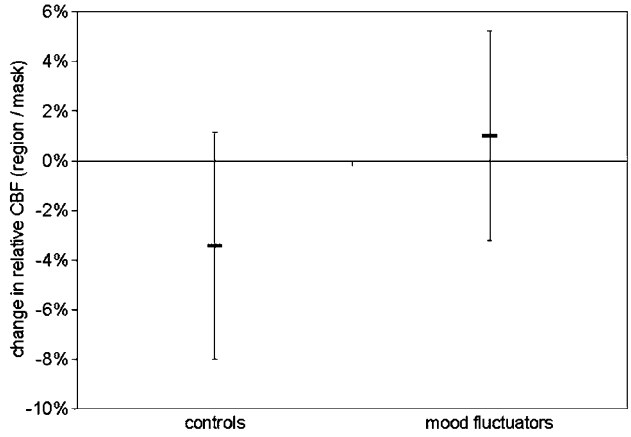

Figure 2 The figures show mean ± SD rCBF in an 8 mm spherical VOI centered at the PCC peak shown in Figure 1, before and after levodopa, in mood fluctuators and in control patients with motor fluctuations only. Note that each VOI includes data from 35 surrounding voxels in addition to the voxel at the statistical peak.

Clinical Observations

There were no significant differences between groups on the baseline characteristics listed in Table 1 ($p > 0.10$), except that mood fluctuators were being treated with a higher total daily dose of levodopa or dopamine agonists ($p < 0.05$).

Clinical ratings of depression and anxiety, based on symptoms during the week prior to the scan, showed a modest overall severity of mood and anxiety, with the mean in the nondepressed range (see Table 4). This is consistent with the clinical description, since episodic, ultradian symptoms define the group of interest, rather than sustained symptoms. Ratings of parkinsonian severity in both groups diminished by roughly half following treatment (repeated measures ANOVA, drug effect $p < 0.005$; $p > 0.20$ for both the diagnosis effect and the interaction), and most subjects had peak-dose dyskinesias (Table 4).

One mood fluctuator patient was crying in the waiting room before the scan. Three mood fluctuators showed hypomanic behavior after levodopa, including euphoria, flirting or inappropriate sexual comments, silly or giddy behavior, joking, and talkativeness. Severity was mild, with Bech mania scores of 1.5, 2, and 4. One patient showed severe wearing-off bradyphrenia, trailing off to mutism while answering a question, only to spontaneously finish the sentence 10 min later during levodopa infusion. One additional mood fluctuator patient said 'I feel like I took an upper.' One control subject felt mood had improved and another denied change in mood *per se* but said 'mentally, I feel better.'

Surprisingly, several mood fluctuator patients did not have marked sadness and anxiety during the baseline scans, and baseline mood ratings did not differ between patient groups (Table 4). Patients told us they felt emotionally better during the study baseline than during their usual off periods, and this was confirmed by their caregivers. Based on their comments and our observations, we speculate that the constant personal attention we provided during the study somewhat reduced the severity of their off-period anxiety and depression. To a small extent, the modest severity of baseline symptoms on the study day may also

Table 3 Most Significant Regional Differences in Levodopa Response in the Mood Fluctuators > Motor Fluctuators Comparison

Cluster *p*(cor)	No. of voxels	Voxel's *t*	*x,y,z* (mm)	Description	BA
0.009	662	4.53	−2,−26,54	Medial frontal gyrus	6
		3.79	−6,−26,34	Posterior cingulate	31
0.513	75	3.68	60,−54,10	Superior temporal gyrus	22
0.163	221	3.68	68,−28,24	Inferior parietal lobule	40
0.733	30	3.49	−50,14,−2	Inferior frontal gyrus	22
0.607	54	3.47	48,−20,14	Insula	13
0.803	18	3.42	−4,−38,10	Splenium/posterior cingulated	—
0.647	46	3.40	−52,−54,16	WM deep to superior temporal gyrus	22
0.474	85	3.40	−24,50,−12	Middle frontal gyrus	11
0.797	19	3.35	−44,−20,10	WM deep to transverse temporal gyrus	13

Most significant clusters of contiguous voxels with $t > 3.17$ (100 df), and local maxima within each cluster separated by more than 8 mm (Figure 1).
p(cor): *p*-value corrected for multiple comparisons; no. of voxels: number of contiguous voxels in each cluster; *x,y,z*: Talairach atlas coordinates; BA: Brodmann area. Voxel volume = 8 mm^3.

Table 4 Scan-Day Symptoms

	Mood fluctuators	Controls
Ham-D	8.3 ± 4.9	5.0 ± 4.6
Ham-A	8.9 ± 4.8	5.8 ± 2.6
Mood VAS ratings during scans (mm)		
Sad (0)–happy (100), baseline	61 ± 23	58 ± 14
Sad (0)–happy (100), levodopa	86 ± 12	71 ± 13
Modified UPDRS (maximum = 32)		
Baseline	7.1 ± 3.7	11.8 ± 9.3
Levodopa	4.1 ± 1.7	6.5 ± 3.7
Number with dyskinesias after levodopa	6	10

Table 5 Mood Fluctuation Subtype and PCC Response to Levodopa

Off depression	Off anxiety	On mania	PCC response (%)
N	Y	N	−5.0
N	N	Y[a]	−1.7
N	N	Y	−.5
Y	Y	N	−1.5
N	Y	Y	+2.4
N	Y	Y	+3.4
Y	Y	N	+3.7
Y	N	Y	+8.3

Additional diagnoses were off-period apathy (1) and off-period bradyphrenia (1).
[a]This patient had on-period hypomania.

reflect a selection bias away from the most severely affected patients: two mood fluctuation patients who came to the PET suite to participate were unable to do so, one due to marked off-period anxiety and the other due to severe off-period neck flexor dystonia. Both patient groups had higher in-scanner mood scores on levodopa (ANOVA, significant effect of levodopa, $p < 0.001$), but the increase was twice as great in the mood fluctuators (interaction of diagnosis and levodopa status, $p = 0.12$; *post hoc* two-tailed *t*-test, $p = 0.02$; see Table 4).

Levodopa Plasma Concentrations

Mean plasma concentrations increased from 132 ± 177 ng/ml at baseline to 1590 ± 513 ng/ml after levodopa administration. There was no significant difference between groups in levodopa plasma concentrations either before or after drug.

Subgroup Analyses

We examined whether it was likely that factors other than the mood fluctuation diagnosis affected the most significant result in our primary PET analysis. First, some subjects in each group received levodopa by mouth rather than i.v. Ignoring these subjects, the mean PCC rCBF response was −3.5% (controls) *vs* +1.3% (mood fluctuators), similar to the means for all subjects at −3.6% (controls) and +0.8% (mood fluctuators). Thus the route of administration seems to have had little effect on the main result. Second, one subject in each group was scanned on the 953b scanner. Ignoring those two subjects, the mean PCC rCBF response was −3.9% (controls) and 1.3% (mood fluctuators), again suggesting no meaningful difference. Third, the mood fluctuation group included patients with various combinations of off-period depression, off-period anxiety, and on-period mania or hypomania. The possible effect of mood fluctuation subtype on PCC rCBF response to levodopa is shown in Table 5; the numbers are too small and the pattern too irregular for definitive conclusions, but the most 'typical' response (ie the highest) for the mood fluctuator group is in the only subject with both off-period depression and on-period mania, while the most atypical (ie the most negative) response was in the only subject with neither.

Finally, some subjects in each group were taking an antidepressant (Table 1). Apparently antidepressants alone do not explain the group difference in PCC response to

levodopa, since within the motor fluctuator control group the response was similar regardless of antidepressant exposure (antidepressant, $N=5$, -3.8%; none, $N=8$, -3.4%). Mood fluctuators differed more, but neither subgroup approached the responses of the controls (antidepressant, $N=6$, $+1.4\%$; none, $N=2$, -0.9%).

DISCUSSION

Baseline Differences in Resting rCBF in Mood Fluctuators

To our knowledge, no other anatomic or functional imaging studies have compared PD patients with and without levodopa-related mood fluctuations. Published comparisons of regional resting brain metabolism or rCBF between PD patients with and without (nonfluctuating) major depression have shown decreased activity of caudate nuclei and prefrontal cortex (Mayberg *et al*, 1990; Jagust *et al*, 1992; Mayberg, 1994; Ring *et al*, 1994). The decreased caudate activity likely represents a true decrease per unit volume rather than a partial volume effect (Lisanby *et al*, 1993, p 18). In a before- and after-treatment FDG PET study of depressed PD patients, an antidepressant response to fluoxetine was associated with a metabolic increase in dorsal anterior cingulate regional metabolism and a metabolic decrease in ventral anterior cingulate (Stefurak *et al*, 2001; Mayberg, 2003). None of these differences were detected in the mood fluctuators, in whom baseline rCBF differed only at a few voxels over 3 cm away.

Regional CBF Response to Levodopa in the Whole Sample

The responses to levodopa in the combined patient sample largely replicate those we previously observed in three separate samples of PD patients as well as in healthy controls (Hershey *et al*, 1998, 2003). The large brainstem response to levodopa or dopamine agonists has been reported in various species, and involves a diffuse midbrain area even when assessed at much higher image resolution using [^{14}C]2-deoxyglucose and *ex vivo* film autoradiography (Trugman and Wooten, 1986; Grasby *et al*, 1993; Kapur *et al*, 1994; Hershey *et al*, 2000; Black *et al*, 2000). In the rodent studies, the response includes superior colliculus, midbrain reticular formation, and subthalamic nucleus. Other levodopa-responsive regions in Table 3 (eg parahippocampal gyrus, insula, and lateral orbital cortex) were not reported in our previous studies of levodopa activation, and may also mediate dopaminergic influences on mood or cognition. Together, these studies provide substantial information on the functional responses to levodopa in normal and parkinsonian humans.

Other groups have also reported levodopa activation imaging studies in PD, as reviewed in part by Hershey *et al* (2003). An early PET study found no rCBF differences after levodopa in 10 motor fluctuators (Melamed *et al*, 1986). Feigin *et al* (2001) report an FDG PET levodopa activation study in seven PD patients. As in the present study, they found a statistically modest decrease in activity in cerebellum. Similar decreases occurred in putamen, thalamus, and primary motor cortex; these likely would not have been identified in our study due to differences in statistical threshold and axial field of view. Berding *et al* (2001) report a similar study in 11 PD subjects; regional metabolism decreased in orbital cortex (peak change was 12 mm from the peak in Table 2). Neither study detected regional increases, which may relate to sample size or differences in levodopa challenge.

Regional CBF Response to Levodopa in Mood Fluctuators *vs* Motor Fluctuator Controls

The primary PET analysis shows that the brain's regional response to levodopa is significantly different in PD patients with levodopa-dose-related emotional changes, compared to similar patients with fluctuations only in motor function. The rCBF response to levodopa detected group differences not evident in the group comparison of baseline resting rCBF.

The most significant group difference in rCBF response to levodopa occurred in a contiguous medial cortical region containing a superior and an inferior peak. The superior peak (BA6) may reflect group differences in motor cortex innervation by dopamine-influenced neurons, and may be important to mood fluctuations or may represent imperfect group matching on motor features of PD (although the groups compared very closely on duration of illness, clinical ratings of parkinsonism, and prevalence of levodopa-induced dyskinesias). The other peak is centered in PCC, which has previously been shown to be abnormally active in depression or anxiety. This region probably includes BA31 (Talairach and Tournoux, 1988) and retrosplenial cortex, which in primates extends this far anteriorly along the corpus callosum (Parvizi *et al*, 2003).

Posterior Cingulate Cortex

In a PET study of major depression, metabolism in this part of PCC (peaks at (−8,−32,30) and (6,−26,32)) significantly increased in patients who responded to 6 weeks of fluoxetine treatment, but significantly decreased in nonresponders (Mayberg *et al*, 2000). Posterior cingulate metabolism had decreased in both groups after 1 week of fluoxetine treatment, before depression improved. In other words, activity of PCC was a state marker for remission of major depression (increase), and for nontherapeutic exposure to fluoxetine (decrease). Similar results were observed over a much shorter time scale in an rCBF study of induced sadness or anxiety in normal volunteers (Liotti *et al*, 2000). Decreased activity was observed during anxious and depressed states in PCC, with peak differences at (6,−64,17) and (3,−40,20), somewhat posterior and inferior to those seen here.

PCC activity is also linked to anxiety in different model conditions. Breathlessness and air hunger induced by inhalation of 8% CO_2 caused decreased PCC blood flow with peak change at (0,−36,32) (Brannan *et al*, 2001), and there was an $\sim$5% decrease in PCC rCBF in volunteers who were anxious while awaiting a painful shock to the hand (did not reach statistical significance using conservative methods) (Simpson *et al*, 2001). In studies of post-traumatic stress disorder that provoked anxiety by presenting trauma-related pictures and sounds, activations or deactivations

were found in PCC (Shin *et al*, 1997; Bremner *et al*, 1999a, b; Liberzon *et al*, 1999). As in our study, Bremner *et al* (1999b) found that posterior cingulate activation in patients was sometimes of opposite sign than in healthy controls.

From such studies, Liotti *et al* (2000) concluded, 'it is clear that the posterior cingulate plays a critical role in the regulation of both normal and pathologic negative emotions' (p 36). In fact, Maddock (1999) noted that after inferior prefrontal cortex, PCC (including retrosplenial cortex) was the brain region most consistently activated in 51 functional neuroimaging studies of emotion. The specific role PCC plays in emotion is not clear, but available data suggest that it may encode the emotional significance of stimuli, perhaps by mediating the comparison of present percepts to emotions associated with episodic (eg autobiographical) memory (Maddock, 1999).

The rCBF response in posterior cingulate may arise either from neurons intrinsic to PCC or from afferent projection axons terminating in PCC. Afferents to PCC include contralateral PCC; ipsilateral anterior cingulate cortex (dorsal and ventral), posterior parietal cortex, superior temporal sulcus (STS), parahippocampal gyrus, ventral claustrum, and both orbital and dorsal prefrontal cortex; certain thalamic nuclei (pulvinar, lateral dorsal, anterior dorsal, anterior ventral); raphe nuclei and locus ceruleus; and the rostral medial anterior portion of caudate nucleus (Vogt *et al*, 1979, 2003; Baleydier and Mauguiere, 1980; Van Hoesen *et al*, 1993; Parvizi *et al*, 2003). These regions may help explain how PCC is modulated by dopamine or mood.

Dopaminergic modulation of PCC metabolism and blood flow may arise directly from the caudate, which receives a heavy dopaminergic innervation. However, dopamine could influence PCC indirectly via other brain regions. For instance, in a primate model, the most significant effects on rCBF after administration of a dopamine agonist occurred in STS after a D1 agonist and in orbital prefrontal cortex after a D3-preferring agonist (Black *et al*, 1997, 2002b). Both regions project to PCC. In any case, levodopa and several dopamine agonists clearly affect PCC rCBF (Friston *et al*, 1992; Black *et al*, 2002a, b; Hershey *et al*, 2000).

Afferents to PCC may also contribute to the relationship of emotion with PCC rCBF. For example, metabolism in both rostral and ventral portions of anterior cingulate cortex is abnormal in major depression (Drevets, 2001; Mayberg, 1997). Patients with familial pure major depression show decreased rCBF, metabolism, volume, and glial cell number in subgenual anterior cingulate cortex (Drevets *et al*, 1997; Öngür *et al*, 1998). Thus an altered PCC response to dopamine in patients with mood fluctuations may reflect abnormal dopaminergic modulation of caudate, anterior cingulate, or prefrontal cortex. One possible mechanism could be differential loss of dopamine innervation to these nuclei; no data directly address this possibility, but Torack and Morris (1988) did find greater cell loss in ventral tegmental area in PD patients with an antemortem diagnosis of depression.

PCC: A Hypothesis

The motor fluctuator controls responded to levodopa with a decrease in PCC rCBF, an apparently normal response replicated by D2-like agonists (Hershey *et al* 2000; Black *et al* 2002a, b). Decreased PCC activity is often associated with anxiety or sadness (Mayberg, 2003), but must not be sufficient to produce these emotions since levodopa and D2-like agonists do not usually cause anxiety or sadness. We speculate that dopaminergic pathways that affect PCC activity may mitigate extremes of mood. The mood fluctuators' loss of the PCC response to levodopa may thus be related to their clinical experience of emotional extremes. The valence of the dopamine-related mood changes may be determined by activity in other, anatomically connected, areas of the brain such as anterior cingulate or orbital cortex.

Other Group Differences in rCBF Responses to Levodopa

Several other regions showed a more positive response to levodopa in mood fluctuators. These included regions near STS, the inferior parietal lobule, the insula, and orbital frontal cortex (Table 2 and Figure 1). Lateral orbital cortex (BA11) is strongly implicated in regulation of mood and impulsivity, receives striatal afferents, and is influenced by dopamine, suggesting that this region may be relevant to the mood and anxiety fluctuations that differentiate our two groups of patients (Öngür and Price, 2000; Black *et al*, 2002b). A PET study of major depression identified rCBF in posterior inferior parietal lobule as correlated with anxiety (Grasby *et al*, 1993). In several studies, decreased metabolic activity in inferior parietal cortex (BA40) corresponds highly with state sadness or with an anxiety disorder, but the peak in Table 2 is at least 26 mm from these regions (Mayberg *et al*, 1999; Bremner *et al*, 1999a, b). Levodopa does decrease inferior parietal blood flow in patients and normal controls (Hershey *et al*, 2003). Several studies of sadness or anxiety have detected abnormal activity of insula, primarily but not exclusively anterior insula (Malizia, 1999; Mayberg *et al*, 1999). There is no obvious relationship of STS or surrounding cortex to mood regulation, but STS rCBF is affected by dopamine agonists (Black *et al*, 2000).

A cluster of voxels in hippocampus and parahippocampal gyrus reacted in the opposite direction (more negative response to levodopa in mood fluctuators, $p < 0.08$). The potential role of the hippocampus in idiopathic major depression has been reviewed recently (Sheline *et al*, 2002; Mayberg, 2003). Chronicity of major depression is associated with decreased hippocampal volume (Sheline *et al*, 1996). Furthermore, in serotonergic treatment of major depression, either with or without PD, hippocampal activity decreases with treatment response but increases with treatment failure (Mayberg, 2003). This pattern is not seen with response to cognitive therapy or placebo, however. Conceivably, the greater decrease in hippocampal activity with levodopa in mood fluctuators corresponds to the greater improvement in mood in these subjects.

Pharmacology

The relationship of dopamine to (nonfluctuating) depression in PD is unclear (Bunney *et al*, 1969; Jouvent *et al*, 1983; Mayeux *et al*, 1986; Torack and Morris, 1988;

Cummings, 1992; Kostic *et al*, 1996; Black and Pandya, in press). By contrast, levodopa-related mood fluctuations in PD have a strongly face valid relationship to brain dopamine concentrations. Dopaminergic effects on mood are well documented and have been reviewed elsewhere (Drevets *et al*, 2001; Klimek *et al*, 2002; Racette *et al*, 2002). However, there is little direct evidence as to what receptor subtype(s) may mediate dopamine's modulation of emotional symptoms or rCBF in these mood fluctuation patients.

Recent pharmacologic activation PET studies in a primate model may shed light on this question. The activation of PCC rCBF by levodopa is replicated by D2-like dopamine agonists, but not by a D1 agonist (Black *et al*, 2000, 2002a, b). Similarly, lateral orbitofrontal cortex was strongly activated in normal baboons by the D3-preferring agonist pramipexole (Black *et al*, 2002b), and superior temporal gyrus is strongly activated by a D1 agonist (Black *et al*, 2000). Further study will be required to confirm whether PD patients with mood fluctuations have more pronounced mood responses to D2-like than to D1-like dopamine agonists, or whether the imaging findings in this levodopa activation study can be replicated with specific agonists.

Clinical Results, Limitations, and Future Directions

The two study groups were defined by a clinical history of mood fluctuations. In the PET scanner, the two groups had only modest differences in mood ratings. In interpreting the imaging results, this observation reduces the possible confound of state-related group differences during the scan session. A similar dissociation between usual clinical response outside the scanner and clinical observations in the experimental setting benefited our prior levodopa challenge PET study of drug-induced dyskinesias (Hershey *et al*, 1998). However, state-related changes in mood may be examined if larger in-scanner fluctuations of mood are observed in future patients.

The small number of subjects makes the study vulnerable to Type II errors. For instance, previous studies of resting regional brain metabolism in PD detected significant abnormalities in patients with major depression (Mayberg *et al*, 1990). Mood fluctuators were taking more levodopa and dopamine agonists, but this likely reflects efforts to treat off-period psychiatric symptoms, given the comparable off-period motor signs and duration of illness (Table 1). Additional limitations of this study include the potential for unidentified clinical differences between groups, and the heterogeneity in clinical and study procedures addressed in Results. Also, regional blood flow is an indirect measure of regional metabolism and neuronal function, and its interpretation depends on the tight coupling between rCBF and regional metabolism. This coupling is preserved even in the presence of non-ergot dopamine agonists (McCulloch *et al*, 1982), and is likely even more stable in our experiment, since with levodopa/carbidopa, dopamine production outside the brain is blocked and levodopa has no net effect on whole-brain blood flow (Hershey *et al*, 1998, 2000, 2003).

Our results demonstrate the utility of the pharmacologic activation approach in studying neuropsychiatric illness: although PCC has known dopamine-influenced afferents and known association with emotional regulation, it has not previously been considered in discussions of levodopa-related mood fluctuations in PD. Also, in the absence of pharmacologic stimulation, no baseline difference in PCC rCBF was identified. Future clinical, neuroimaging, and pathological studies may clarify the pathophysiology and pharmacology of PCC with respect to levodopa-mediated effects on mood.

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APPENDIX

Criteria Used to Diagnose 'Clinically Significant Dopa-Related Mood Fluctuations'

a. Marked anxiety, sadness, or mania, nearly always occurring at a predictable time relative to doses of dopamimetic medication.
b. Diagnosis follows

1. corroboration of history by spouse or other informant, and
2. thorough neurological and psychiatric examination by a clinician experienced in evaluating mood symptoms in PD patients.

c. The symptoms cause clinically significant distress, or impairment in social, occupational, or other important areas of functioning.
d. The symptoms are not better accounted for by another syndrome, including major depression (ie while experiencing above symptoms, patient must have normal mood and interests most of the time for at least a month), pathological crying, or pure apathy; and are not more parsimoniously attributable to PD without depression (eg facial hypomimia, isolated fatigue, 'internal tremor' without other evidence of anxiety, or akathisia or tremor that the patient misidentifies as 'anxiety').

A Screening Interview in a PD Patient Diagnosed with Clinically Significant Mood Fluctuations (Summary, Based on Contemporaneous Written Notes)

First, the examiner established that the effect of each dose of levodopa often wore off before the next dose was due, despite successive changes in the dosage of levodopa/carbidopa, switch to the sustained-release form, and addition of ropinirole and later tolcapone. Then, the examiner asked, 'What symptoms do you notice when your medicine wears off?' The patient replied, 'I have some stiffness, [pause] but what markedly changes is my mental attitude. I get depressed feeling and incapable of doing hardly anything.' On follow-up questions, he described feeling at those moments sad, blue, tearful, tense, and worried, with a 'negative attitude,' low energy, and poor concentration. At those times, 'I question whether life is worth living.' He was able occasionally to nap at these times. After taking his next dose of medication 'it kicks in about 30 min later and I feel good again.' A semistructured psychiatric interview (Hudziak *et al*, 1993) revealed no additional psychiatric symptoms except as follows. He twice had developed transient hallucinations in late life, once after surgery and once after addition of an unknown antiparkinsonian medication. He had a fear of heights starting in his 40s without significant distress or impairment. He had had no significant depressive symptoms until 10 years after the diagnosis of PD. At 3 years prior to study participation, after the death of his wife, he developed frequent sadness and initial or middle insomnia but (except when 'off') had normal appetite, normal concentration, no excessive guilt, no serious thoughts of suicide, and generally intact interests. He had never met research criteria for major depression.