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Depression in Parkinson's Disease
A Positron Emission Study

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Background. This study investigated biological correlates of depression in patients with idiopathic Parkinson's disease (PD). We tested the hypothesis that in patients with PD and depression, there was regional dysfunction involving brain areas previously implicated in functional imaging studies of patients with primary depression.

Method. Using positron emission tomographic measurements of regional cerebral blood flow (rCBF), patterns of resting rCBF were measured in ten patiens with PD and major depression, and ten patients with PD alone. The results were compared with findings from ten patients with primary depression and ten normal controls, scanned using identical methods as part of an earlier study. Groups were matched for age, sex and symptom severity.

Results. Bilateral decreases in rCBF were observed in anteromedial regions of the medial frontal cortex and the cingulate cortex (Brodmann's areas (BA) 9 and 32) in the depressed PD group, compared with those with PD alone and compared with normal controls. This regional disturbance overlapped that observed in patients with primary depression.

Conclusions. The findings indicate that the medial prefrontal cortex is a common area of neural dysfunction in the manifestation of both primary depression and depression in PD.

Depression is a frequent psychiatric disturbance in patients suffering from Parkinson's disease (PD). The reported rate of depression in PD varies considerably, ranging from 4% to 70% (Cummings, 1992). More rigorous investigation suggests that while depressive symptoms are common, depression meeting diagnostic criteria is less frequent (Brown & MacCarthy, 1990).

There is evidence that depression in PD has a biological basis. Firstly, depressive episodes may antedate the development of motor symptoms of PD (Fukunishi *et al*, 1991). Secondly, severity of depression does not correlate with specific measures of motor impairment (Starkstein *et al*, 1990). In addition, patients have remained depressed in spite of significant improvement in their motor functioning after levodopa treatment (Marsh & Markham, 1973). As degeneration of serotonergic and noradrenergic projections occurs alongside degeneration of dopaminergic neurons in PD, it has been suggested that depression in such patients is associated with a widespread monoaminergic disturbance (Fibigier, 1984; Mayeux, 1990).

Functional imaging studies of primary depression have demonstrated focal disturbances of frontal lobe activity (Baxter *et al*, 1989; Bench *et al*, 1992), leading to suggestions that these regions are associated with the manifestation of depression. Specific regional dysfunction may be related to specific clinical manifestations of depression (Bench *et al*, 1993). Studying depression arising in different clinical contexts may provide additional information on the cerebral correlates of depression in two ways. Firstly, comparison of two patient groups who share the same behavioural characteristics, but who otherwise have different diagnoses, allows more precise interpretation of the significance of functional disturbances. Secondly, if depression occurring in different diagnostic groups is associated with similar functional abnormalities, then this provides strong corroboration that a particular regional deficit is indeed critical in the manifestation of depressive states.

In this study we wished to test two related hypotheses. First we hypothesised that in two groups of patients with equally severe PD there will be an area of regional cerebral dysfunction unique to the depressed group. Secondly, this regional dysfunction will involve some or all of the brain areas previously implicated in functional imaging studies of patients with primary depression.

Method

Study design

Using positron emission tomography (PET) we measured resting state regional cerebral blood flow (rCBF) in two age- and sex-matched groups of patients with PD, one group with moderately severe depression (meeting DSM–III–R criteria for a major depressive episode; American Psychiatric Association, 1987), and the other without depression. The two groups were also matched for severity of PD (Hoehn & Yahr, 1967). In order to facilitate comparison of

the findings in the depresed PD group with the results of an earlier study of patients with primary depression (Bench *et al*, 1992), the findings of the depressed PD group were also compared directly with an age- and sex-matched group of normal controls who formed part of the comparison group in that earlier study. In addition, rCBF data from a subgroup of these patients with primary depression, age- and sex-matched to the PD groups, was compared with the results from the depressed PD group.

Subject selection

Patients with PD were recruited from two specialist movement disorder clinics where a clinical diagnosis of idiopathic Parkinson's disease had been made according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria. Only PD patients without dementia, and with normal cognitive function as defined by a score on the Mini-Mental State Examination (MMSE) of 27 or more (Folstein *et al*, 1975), were selected. Non-depressed PD subjects selected had no history of depression.

The PET rCBF scans of normal controls and patients with primary depression that were used were not initially obtained for this study but were drawn from an earlier study of PET and depression (Bench *et al*, 1992). The scans were chosen from that larger pool of subjects on the basis of being most closely matched in age to the subjects in the PD groups. None of these subjects had a history of organic brain disease or significant medical illness. Ten subjects were included in each group (see Table 1). The subjects with primary depression in Bench's study also met DSM–III–R criteria for a major depressive episode (American Psychiatric Association, 1987).

All Parkinsonian subjects were receiving anti-Parkinsonian medication in routine regimens unchanged by the study. Four of the depressed PD patients were taking antidepressant medication.

The study was approved by the ethical committees of all referring hospitals and by the local committee of the Hammersmith Hospital, where the scans were performed. Permission to administer $C^{15}O_2$ was granted by the Administration of Radioactive Substances Advisory Committee (ARSAC). All subjects gave informed written consent.

Patient assessment

All subjects received a clinical psychiatric assessment from which the DSM–III–R diagnosis was made. Severity of mood disturbance in the PD groups and the depressed patients was also measured using the 17-item Hamilton Depression Scale (HDS: Hamilton, 1960). Only subjects scoring 19 or more were included in the depressed group. Non-depressed PD patients were defined as those with no significant depressive symptoms elicited on clinical assessment by a neuropsychiatrist (HAR), and who scored in the non-depressed range of the HDS.

The stage of PD was described using the Hoehn & Yahr (1967) scale. The characteristics of the subjects are described in Table 1. All the ratings described were obtained on the day of the PET scan.

Scanning procedure

All subjects underwent steady-state measurement of cerebral blood flow using $C^{15}O_2$ as previously described (Frackowiak *et al*, 1980). Studies were performed using a PET scanner (CTI Knoxville model 931-08/12). The physical performance of this scanner has been described elsewhere (Spinks *et al*, 1988). Measured attenuation corrections were made with the ratio of counts in blank and transmission scans obtained using a ^{68}Ge ring source. Emission scans were reconstructed using a Hanning filter with a cut-off frequency of 0.5 cycles per pixel. After reconstruction and filtering, the pixel size was 2.05 mm^2 and the image resolution $8.5 \times 8.5 \times 7.0$ mm. Fifteen tomographic slices were obtained simultaneously.

All studies were performed in the supine position in a room with dimmed lights and minimal environmental noise. Subjects were asked to close their eyes during the scans. For each subject a polystyrene head mould was made which was used to ensure correct positioning in the scanner and relative head immobility. A 22 g Teflon cannula was inserted into a radial artery after Allen's test for collateral circulation and infiltration of the skin with 1% Marcain (bupivicaine). The subjects were aligned in the scanner with reference to a laser beam system so that the detectors were parallel to the orbito-meatal line. $C^{15}O_2$ was administered by inhalation. For the estimation of CBF, subjects inhaled $C^{15}O_2$ (0.75 MBq/ml, flow rate 500 ml/min) for 18 minutes. Three arterial blood samples were taken during each emission scan. These samples were centrifuged, and plasma and whole-blood activity measured in a well counter, cross-calibrated with the PET scanner. Two arterial samples were taken for estimation of haemoglobin, pCO_2 and pO_2. Using this information, the raw emission data were transformed into parametric images of CBF.

Data analysis

Image analysis was performed to allow within-group averaging of subject data, followed by between-group

comparisons, all on a pixel-by-pixel basis. Analysis utilised SPARC workstations (Sun Microsystems Europe) using an interactive image analysis software package (ANALYZE 3.0, Biodynamic Research Unit, Rochester, MN, USA). Functional images were checked for artefacts and corrected for yaw and roll. The 15 original planes of data (6.75 mm interplane distance) were transformed to 26 planes in standard stereotactic space (Talairach & Tournoux, 1988). In this space each pixel represents 2×2 mm, and transaxial planes are 4 mm thick. Images were smoothed using a 1.8 cm Gaussian filter to minimise the effects of normal variations in gyral anatomy (Friston *et al*, 1991).

For each group comparison the stereotactically normalised cerebral blood flow images were adjusted for individual differences in global blood flow using an analysis of covariance (Friston *et al*, 1990). This process generated an adjusted mean blood flow map for each of the groups, and an estimate of the error variance for rCBF at each pixel location. Differences in the adjusted group means were assessed using the *t* statistic, so that for each comparison an image of the pixel *t* values was created over all planes of the images for which there were adequate data (Friston *et al*, 1991). The *t* values were displayed as transverse slices and as orthogonal projections within the standard stereotactic space. The threshold for display was set to $P<0.05$ per plane, with a Bonferroni correction for multiple comparisons. This correction corresponded to an expected false positive rate of 1 comparison per 20 planes (Bailey *et al*, 1991), and it is also applied to the data in Table 3. The maximum number of planes analysed in any of the group comparisons, representing the number of planes for which there was complete data, was 15. Figures 1 and 2 therefore indicate those pixels which are sufficiently different, between the two groups in each comparison, to exceed this level of significance. The locations of these pixels are displayed on orthogonal projections and cortical renderings of the brain.

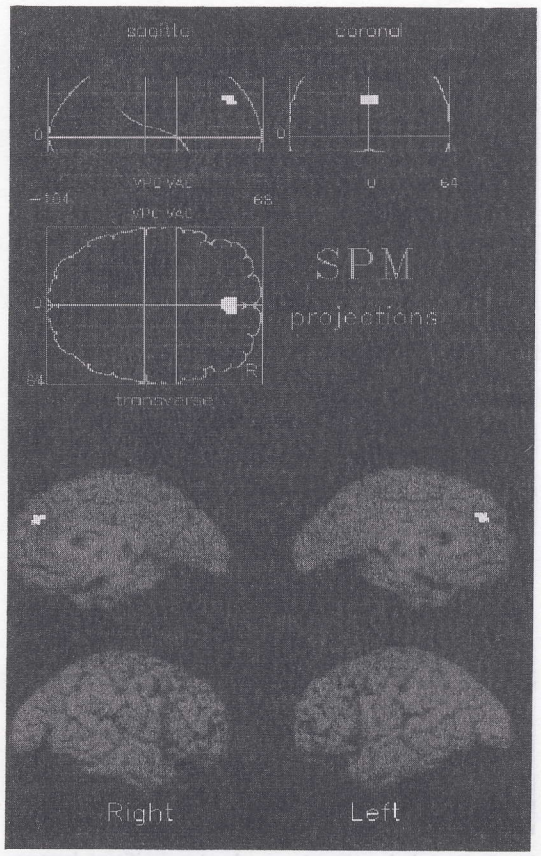

Fig. 1 Statistical parametric map showing significant decreases in rCBF in depressed patients with Parkinson's disease (PDD) compared with those with PD alone. The threshold for display was set to $P<0.05$ per plane, with a correction for the multiple pixels analysed. The highlighted pixels are sufficiently different between the two groups to exceed this level of significance. These pixels are displayed on orthogonal projections and cortical renderings of the brain. The coordinates displayed with the orthogonal projections correspond to the anterior commissure–posterior commissure lines and the limits of the *x* and *y* axes in the atlas of Talairach & Tournoux (1988).

Results

Clinical characteristics

Age and sex distributions were similar across all the groups (Table 1). There were no significant differences between the Parkinsonian groups in MMSE or Hoehn & Yahr scores. The mean HDS score of 22 in the depressed PD group was similar to that recorded by Bench *et al* (1992) in their patients with primary depression, indicating depression of moderate severity. The mean HDS item scores in each of the two depressed groups are given in Table 2. The HDS

Table 1
Study group characteristics

	PD	PD and depressed	Normal	Primary depressed
n	10	10	10	10
Sex (M : F)	6 : 4	6 : 4	6 : 4	6 : 4
Age: mean (s.d.)	64 (10)	62 (13)	66 (10)	64 (10)
HDS: mean (s.d.)	22 (3)	5 (2)	–	24 (5)
MMSE: mean (s.d.)	28 (1)	29 (1)	–	–
H&Y: mean (s.d.)	3.2 (0.5)	3.0 (0.5)	–	–

HDS = Hamilton Depression Scale, MMSE = Mini-Mental State Examination, H&Y = Hoehn & Yahr (1967) scale.

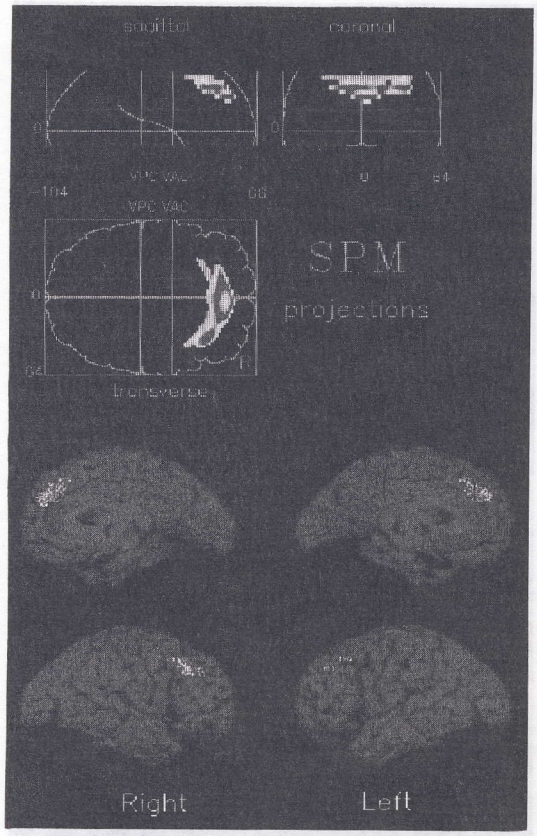

Fig. 2 Statistical parametric map showing significant decreases in rCBF in depressed patients with Parkinson's disease (PDD) compared with normal controls. The threshold for display was set to $P<0.05$ per plane with a correction for the multiple pixels analysed. The highlighted pixels are sufficiently different between the two groups to exceed this level of significance.

scores were by definition significantly lower in the non-depressed PD group (one-way ANOVA, $F=105$, $P<0.000$).

rCBF comparisons

Depressed PD versus PD

This comparison revealed a profile of significantly decreased rCBF in the depressed PD group with respect to the non-depressed PD subjects. The changes were centred on the medial prefrontal cortex bilaterally, involving the medial frontal cortex (Brodmann's area (BA) 9) and the contiguous cingulate cortex (BA 32), extending from 28 to 32 mm above a line joining the anterior and posterior commissures (the AC–PC line). These areas are displayed in Fig. 1. Given in Table 3 are the Talairach coordinates (Talairach & Tournoux, 1988) and adjusted rCBF values, as well as an associated measure of the significance of the difference (the Z score) for the pixels at which there were the most significant differences in blood flow between the two groups. The individual rCBF values at these pixels are displayed as a scatter-plot in Fig. 3.

Table 2
Mean Hamilton Depression Scale scores for primary depressed and Parkinson's disease depressed patients

Item	PD depressed	Primary depressed
Depressed mood	2.4	2.6
Feelings of guilt	2.4	1.1
Suicide	1.6	1.7
Early insomnia	0.9	0.9
Middle insomnia	1.2	0.5
Late insomnia	0.9	1.7
Work & activities	3.1	3.0
Retardation	0.7	1.1
Agitation	1.6	1.7
Psychic anxiety	1.9	2.4
Somatic anxiety	1.3	1.5
Somatic: GI	0.6	0.9
Somatic: general	1.1	1.2
Genital symptoms	0.6	1.4
Hypochondriasis	1.3	1.2
Weight loss	0.7	0.9
Insight	0.4	0.5

GI = gastrointestinal.

Depressed PD versus normal controls

Significant decreases in rCBF in the depressed PD group were observed in the medial prefrontal and anterior cingulate cortices (BA 9 and the anterior portion of BA 32 respectively). These decreases were bilateral but predominantly right-sided (Table 3, Fig. 2, Fig. 4), extending from 24 mm to 44 mm above the AC–PC line.

PD versus normal controls

There were no significant differences between these two groups.

Depressed PD versus primary depression

No differences were observed between the two groups in BA 9 and 32. The only significant difference between the two groups was a small area of decreased flow in the depressed PD subjects in the medial frontal cortex, BA 10, on the right side, present on only one plane at the level of the AC–PC line.

Table 3
Coordinates (Talairach & Tournoux, 1988) of the pixels at which the most significant differences in rCBF were detected between groups

Comparison	Coordinates			Normalised rCBF[1]		
	x	*y*	*z*	PDD	Control	*Z* score[2]
PDD v. PD	0	46	28	46.6	54.8	3.71
	0	44	32	44.1	53.1	3.71
PDD v. normal	4	46	24	51.0	57.8	3.74
	4	46	28	46.4	54.4	4.58
	2	46	32	40.8	48.9	5.04
	34	32	32	43.0	48.9	4.12
	10	42	36	40.2	47.7	4.73
	34	30	36	39.0	46.0	4.63
	4	38	40	40.5	49.3	3.79

1. Adjusted for a global mean blood flow of 50 ml/100 g/min.
2. A measure of the significance of the difference between the groups (the number of standard deviations from the mean *t* value in the (*t*) statistical map of the *t* value for the most significant pixel in the plane). $P<0.05$ Bonferroni-corrected.
PDD = Parkinson's disease with depression.
The *x*, *y*, *z* coordinate system used (Talairach & Tournoux, 1988) represents distances in three dimensions in millimetres from reference lines through the brain. All the data reported here are defined in horizontal brain slices. The *x* axis describes the width of the brain centred around the midline (negative = left, positive = right). The *y* axis describes the length of the horizontal brain slice. It is centred about a vertical orientation plane perpendicular to the anterior commissure drawn through its ventricular margin (negative = posterior, positive = anterior). The *z* axis describes the depth within the brain of the horizontal slice, centred about the anterior commissure–posterior commissure line (negative = superior, positive = inferior).

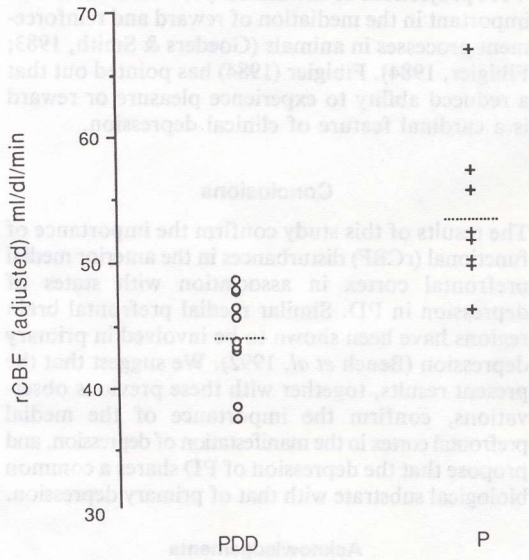

Fig. 3 Individual adjusted rCBF values for depressed–PD (PDD) and PD-alone (P) patients at the pixel of maximum difference between the two groups (0,44,32 in Talairach coordinates).

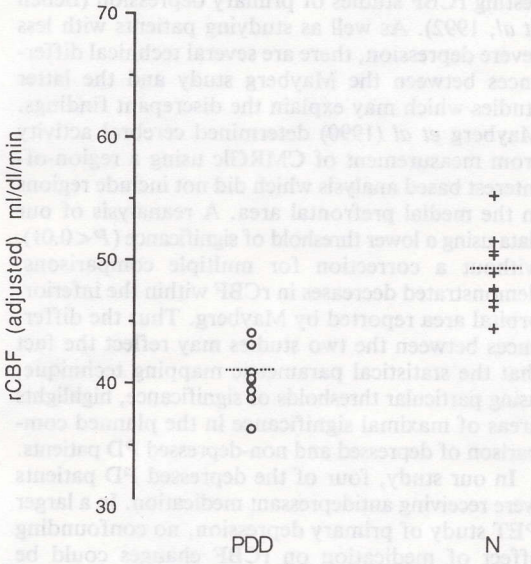

Fig. 4 Individual adjusted rCBF values for depressed–PD patients (PDD) and normal controls (N) at the pixel of maximum difference between the two groups (2,46,32 in Talairach coordinates).

Discussion

The principal finding of this study was of decreased rCBF in Brodmann's areas 9 and 32 in a depressed PD group compared with those with PD alone and with normal controls. There were no significant differences in BA 9 or 32 between the depressed PD group and the patients with primary depression. It may be concluded that decreased blood flow bilaterally in the medial frontal and the cingulate cortices is specifically associated with the presence of depression in association with PD. The absence of a significant difference between the non-depressed PD group and normal controls is in accordance with some (Brooks *et al*, 1992) but not all other PET studies. The significance of the small area of hypoperfusion in BA 10 of the depressed PD group is not clear.

Involvement of prefrontal cortical structures in the manifestation of primary depression has been suggested by several studies. Baxter *et al* (1989) described decreased local cerebral metabolic rates for glucose (lCMRGlc) in the left anterolateral prefrontal cortex in both unipolar and bipolar depression. Bench *et al* (1992) examined rCBF in 33 patients with major depression and observed areas of significantly decreased blood flow in regions of the left dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate

cortex, compared with normal controls. The DLPFC and anterior cingulate regions described in that study overlap with the areas of hypoperfusion in BA 9 and 32 in this study. Bench *et al* (1992) also found an additional region of the left DLPFC to be hypoperfused in their patients with primary depression. This area has been seen to be abnormal in patients with chronic schizophrenia, and Liddle *et al* (1992) have specifically associated hypoperfusion in this area to the syndrome of psychomotor poverty (poverty of speech, flatness of affect and decreased spontaneous movement). These features are also seen in depression, and while they form well recognised symptoms of PD, it may be that DLPFC hypoperfusion is associated with aspects of psychomotor impairment occurring within what are primarily non-motor states. In keeping with this, Bench *et al* (1993) have recently reported a strong association between psychomotor retardation in depression and DLPFC hypoperfusion.

To date, only one other PET study of depression in PD has been published. Mayberg *et al* (1990) measured cerebral metabolic rates for glucose (CMRGlc) in five PD patients with mild depression (mean HDS score of 10.4), four patients with PD alone, and six normal controls. In a region-of-interest analysis they found relative hypometabolism, averaged across both hemispheres, in caudate nuclei and orbital-inferior areas of the frontal lobe (BA 10, 11, 12 and 47) in the depressed PD group. Their results differ from those of this study, and from resting rCBF studies of primary depression (Bench *et al*, 1992). As well as studying patients with less severe depression, there are several technical differences between the Mayberg study and the latter studies which may explain the discrepant findings. Mayberg *et al* (1990) determined cerebral activity from measurement of CMRGlc using a region-of-interest based analysis which did not include regions in the medial prefrontal area. A reanalysis of our data using a lower threshold of significance ($P<0.01$), without a correction for multiple comparisons, demonstrated decreases in rCBF within the inferior-orbital area reported by Mayberg. Thus the differences between the two studies may reflect the fact that the statistical parametric mapping technique, using particular thresholds of significance, highlights areas of maximal significance in the planned comparison of depressed and non-depressed PD patients.

In our study, four of the depressed PD patients were receiving antidepressant medication. In a larger PET study of primary depression, no confounding effect of medication on rCBF changes could be detected (Bench *et al*, 1992). Although all the PD patients were taking anti-Parkinsonian medication, there were no systematic differences between the regimens of the depressed and the non-depressed groups with respect to dopaminergic or anticholinergic medication. In addition, the observation of no differences between rCBF patterns in the pure PD group and unmedicated normal controls supports the assertion that drug effects are unlikely to have contributed to the findings of the study.

As demonstrated in Table 2, the greatest differences in symptoms between the two depressed groups were in the pattern of sleep disturbance and in feelings of guilt. The results indicate that the depressed PD group did not accumulate a greater proportion of their HDS scores on the more somatic items than did the primary depressed group.

Animal studies suggest that disturbed medial prefrontal function may be implicated in the aetiology of depression. In primates, lesions in the target regions of the mesocortical projections, the anterior heteromodal prefrontal cortex, lead to a syndrome characterised by apathy and emotional blunting (Mesulam, 1986). It has been demonstrated that PD patients with major depression, although performing significantly worse than non-depressed PD subjects in a range of cognitive tasks, are particularly impaired on frontal lobe tests (Starkstein *et al*, 1989). Starkstein *et al* (1989) speculate that this dysfunction may be secondary to pathology in the dopaminergic projections from the ventral tegmental area (VTA) to the frontal cortex. It has been demonstrated that dopamine-containing nerve terminals of VTA projections to the medial prefrontal cortex are important in the mediation of reward and reinforcement processes in animals (Goeders & Smith, 1983; Fibigier, 1984). Fibigier (1984) has pointed out that a reduced ability to experience pleasure or reward is a cardinal feature of clinical depression.

Conclusions

The results of this study confirm the importance of functional (rCBF) disturbances in the anterior medial prefrontal cortex in association with states of depression in PD. Similar medial prefrontal brain regions have been shown to be involved in primary depression (Bench *et al*, 1992). We suggest that the present results, together with these previous observations, confirm the importance of the medial prefrontal cortex in the manifestation of depression, and propose that the depression of PD shares a common biological substrate with that of primary depression.

Acknowledgements

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