Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions

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SYNOPSIS We have previously reported focal abnormalities of regional cerebral blood flow (rCBF) in a group of 33 patients with major depression. This report, on an extended sample of 40 patients who demonstrated identical regional deficits to those previously described, examines the relationships between depressive symptoms and patterns of rCBF. Patients' symptom ratings were subjected to factor analysis, producing a three-factor solution. The scores for these three factors, which corresponded to recognizable dimensions of depressive illness, were then correlated with rCBF. The first factor had high loadings for anxiety and correlated positively with rCBF in the posterior cingulate cortex and inferior parietal lobule bilaterally. The second factor had high loadings for psychomotor retardation and depressed mood and correlated negatively with rCBF in the left dorsolateral prefrontal cortex and left angular gyrus. The third factor had a high loading for cognitive performance and correlated positively with rCBF in the left medial prefrontal cortex. These data indicate that symptomatic specificity may be ascribed to regional functional deficits in major depressive illness.

INTRODUCTION

Major depressive disorders are phenomenologically heterogeneous and have diverse clinical manifestations (Andreasen *et al.* 1980). Symptoms include mood disturbance, anxiety, psychomotor change and cognitive deficits (Silfverkiöld *et al.* 1987). Although a disorder of monoaminergic neurotransmission has been widely hypothesized as the critical underlying pathophysiology, no single neurotransmitter deficit has been unequivocally demonstrated. The lack of consistency in findings from biological research in depression is not surprising in the context of its clinical heterogeneity. It is possible that specific syndromes of depression are related to unique neurophysiological disturbances and neurotransmitter deficits (Heninger & Charney, 1987).

The majority of brain imaging studies of

depression have been predicated on the disease model and the assumption that behavioural abnormalities are associated with a specific cerebral dysfunction. As applied to depressive disorders the model hypothesizes an unknown pathophysiology as a cause of the clinical and neuropsychological symptomatology. A major problem with a disease-based or lesion model, particularly in psychiatry, relates to the massive connectivity and distributed nature of neural organization. Although brain systems may demonstrate functional specificity (Lueck *et al.* 1989) it is probable that many functions are topographically distributed (Mesulam, 1990). These systems are composed of local networks, usually confined to a single cytoarchitectonic field (Szentagothai, 1976), and large-scale networks composed of widely distributed and interconnected local networks (Mesulam, 1990). Higher mental functions have been hypothesized to arise from the ensemble actions of these interacting systems (Edelman & Mountcastle, 1977). Such considerations make it plausible that

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depressive disorders are characterized not by a single regional deficit but by distributed dysfunction. Positron emission tomography (PET), with its ability to measure neurophysiological function simultaneously over the entire volume of the brain, is an ideal tool for the *in vivo* investigation of large-scale systems.

To date, studies of primary depression, using functional imaging techniques, have described both global (Mathew *et al.* 1980*a*; Baxter *et al.* 1985; Sackeim *et al.* 1990) and regional (Buchsbbaum *et al.* 1984; Post *et al.* 1987; Baxter *et al.* 1989; Martinot *et al.* 1990; Sackeim *et al.* 1990) changes (usually decreases) in cerebral blood flow and metabolism. Regional disturbances are of particular interest in that they reveal specific neuroanatomical dysfunction. The most consistent regional deficits reported have been decreased cerebral blood flow and metabolism affecting the left dorsolateral prefrontal cortex (Baxter *et al.* 1989; Martinot *et al.* 1990). Other studies have reported multiple areas of regional dysfunction (Sackeim *et al.* 1990). In patients with marked cognitive impairment in the context of a primary depressive illness, so called 'depressive pseudodementia', we have previously described a focal decrease in rCBF in the medial frontal cortex (Dolan *et al.* 1992*a*). Although the findings from these various studies are diverse they can be reconciled with dysfunction within networks that subserve the regulation of mood or behavioural tone.

The scope for delineating dysfunctional systems is limited when using cross-sectional single study designs. Functional systems are characterized by patterns of mutual covariance and repeated study over different functional states is a prerequisite for their characterization. However, the specificity of cross-sectional studies of psychiatric disorders may be increased by relating regional deficits to phenomenological and neuropsychological profiles using correlational analyses. The cross-sectional correlation structure of subjects scanned in the same behavioural state is dependent on experimentally introduced variance effected by subject selection. If subjects exhibit variability in a single behavioural score, for example a psychopathological rating, then brain systems underlying that behaviour can be expected to exhibit neuronal activity which correlates with the behavioural score.

Using statistical parametric mapping (SPM), we have previously reported focal deficits in rCBF, affecting the left anterior cingulate and dorsolateral prefrontal cortices, in a cohort of 33 depressed patients who met Research Diagnostic Criteria (RDC) for major depression (Bench *et al.* 1992). This communication reports on findings from an extended sample of 40 depressed subjects and expands the analysis by describing the relationships between clinical expressions of depression and patterns of rCBF using SPM-based correlation analysis.

METHOD

Patients and controls

A detailed description of the clinical methodology has previously been reported (Bench *et al.* 1992). In summary, 40 patients were recruited from regional acute psychiatric services (North East Thames Regional Health Authority) and a national referral centre (The National Hospital for Neurology and Neurosurgery). After giving informed consent, patients were administered the Schedule for Schizophrenia and Affective Disorders (Endicott & Spitzer, 1978). All patients met the Research Diagnostic Criteria (RDC) (Spitzer *et al.* 1977) for Major Depressive Disorder and scored over 17 on the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). Exclusion criteria included age greater than 75 years, a history of alcohol or substance abuse, significant previous or current medical illness, focal abnormality on CT or MRI scanning or a score of over 4 on the Hachinski ischaemic scale (Hachinski *et al.* 1975).

All patients had normal routine haematological, biochemical and endocrinological indices and physical examinations. Handedness was assessed with a questionnaire (Oldfield, 1971). Medicated patients were entered into the study to allow sampling of a representative depressed group and to enable the assessment of the effects of psychotropic medication on cerebral blood flow. An equal number of medicated and non-medicated patients were recruited. Of the medicated patients, nine were taking tricyclic antidepressants alone and one was taking a monoamine oxidase inhibitor. In the remaining 10 patients medication additional to tricyclics included neuroleptics ($N = 5$), lithium ($N = 2$),

carbamazepine ($N = 1$) and tryptophan ($N = 2$). Further medication in the 24 h preceding the PET scan included temazepam 10 mg ($N = 2$), nitrazepam 5 mg ($N = 1$) and chloral hydrate 500 mg ($N = 2$). Of the unmedicated patients, seven were drug naïve, two had been drug free for more than one year and seven had been drug free for over two weeks. Four patients had stopped unsuccessful or erratic courses of antidepressants at least 2 days prior to the PET measurement. Two of this group had taken low doses of benzodiazepines in the 24 h prior to scanning (temazepam 20 mg). The control group was made up of unpaid normal volunteers. Eighteen were drawn from the library of normal scans available at the MRC Cyclotron Unit and five were recruited prospectively by local advertisement. None of the controls had a history of neurological or psychiatric illness, nor were they taking psychotropic medication at the time of scanning. Ethical approval was obtained from all referring hospitals and locally from the Royal Postgraduate Medical School Research Ethics Committee. Permission to administer radioisotopes was obtained from the Administration of Radioactive Substances Advisory Committee of the United Kingdom.

Factor analysis of clinical data

To explore the relationship between depressive symptomatology and rCBF the clinical data were transformed, using factor analysis, into a limited number of psychopathological dimensions. These were then correlated with the regional CBF in the depressed group. This approach was implemented so as to reduce the number of correlations made and decrease the likelihood of type I errors. The symptom scores entered into the factor analysis were derived from scores for individual items in the SADS and the total MMSE score. Factor analysis was performed using the Statistical Package for Social Sciences for IBM compatible Personal Computers (SPSS/PC+). Principal components extraction of factors was followed by varimax rotation. The factor scores were calculated using the regression method.

PET methods

Regional cerebral blood flow was measured under resting conditions in the supine position in a quiet darkened room. Subjects were posi-

tioned in the PET scanner (CTI model 931-08/12) (Spinks *et al.* 1988) with reference to a laser system so that the detectors were parallel to the orbito-meatal line. Relative immobility and comfort were established using an individually moulded polystyrene head rest. Subjects were asked to close their eyes during the examination but no other instructions were given. ^{15}O xygen in the form of C^{15}O_2 was administered via a light plastic face mask according to a well-established protocol (Frackowiak *et al.* 1980). A single scan was acquired over the final 10 min period of an 18 min inhalation and arterial blood samples were taken via an indwelling 22 g catheter at 0, 5 and 10 min into the acquisition period. A Hanning filter with a cut-off frequency of 0.5 was used in the reconstruction of the images giving a transaxial resolution of 8.5 mm. The raw data were transformed into parametric images (Frackowiak *et al.* 1980) and prepared for subsequent analysis. All scans of patients and controls were performed on the same equipment and using the same methods over a three-year period up to June 1991.

Image analysis

Statistical parametric mapping

Statistical parametric mapping refers to a series of techniques for analysing functional images, using a pixel by pixel approach, that have been developed at the MRC Cyclotron Unit, at the Hammersmith Hospital, London (Friston *et al.* 1991b; Friston & Frackowiak, 1991). The series of data transformations that make up these methods aims to increase sensitivity by minimizing error variance. Statistical parametric mapping uses a variety of statistical techniques, the end result being a statistical parametric map (SPM). SPMs can be viewed as images of change significance where each pixel value is a statistical quotient, such as a t value.

Initial data transformation

The original 15 planes of data acquired from the scanner (6.75 mm interplane distance) were interpolated to 43 planes. This rendered the voxels approximately cubic with a pixel size of $2.05 \times 2.05 \times 2.25$ mm. The scans were then stereotactically normalized. First, positional differences between images were removed by reorientating and translating them with reference to the inter-commissural (AC-PC) line. The

AC-PC line was identified from anatomical information within the primary PET image (Friston *et al.* 1989). Further transformation of the image into the standard stereotactic space was performed by matching with standard PET templates derived from $C^{15}O_2$ scans of normal volunteers. This matching occurred in 3 dimensions (x , y and z), using both linear rescaling (for size) and non-linear resampling of data (for shape) (Friston *et al.* 1991a). The image volume was then resliced into the standard brain volume (Talairach & Tournoux, 1988) so that the interplanar distance was 4 mm with pixel size 2×2 mm and the reference (AC-PC) plane was at 0 mm. The images were smoothed with a Gaussian filter in all 3 dimensions in order to reduce further the error variance associated with individual variability in gyral anatomy and to increase the signal to noise ratio.

Categorical comparisons

For each categorical comparison the stereotactically normalized CBF images were adjusted for individual differences in global blood flow using an analysis of covariance (ANCOVA) (Friston *et al.* 1990). This procedure generated an adjusted mean blood flow map for each group (e.g. depressed and controls) and an estimate of the error variance for the 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. The t statistical parametric maps (SPM $\{t\}$ s) were thresholded with a correction for non-independent multiple comparisons that corresponded to an expected false positive rate of one focus per 20 planes (Bailey *et al.* 1991).

Dimensional comparisons

To examine changes in rCBF which correlated with clinical scores, a within (depressed patient) group pixel by pixel linear regression of rCBF on global flow was first performed to remove the confounding effects of global blood flow (Friston *et al.* 1990). This procedure generated 40 new images whose global flow had been adjusted to 50 ml/100 g/min but whose regional profile was preserved. This adjusted profile of pixels was correlated with the three clinical factor scores derived from a factor analysis, described below. Pixels at which the 40 adjusted rCBF values

showed significant ($P < 0.01$) correlations with the three factors were identified. Only SPMs for which the total number of significant correlations exceeded that expected by chance, as assessed by the χ^2 statistic, are reported ($P < 0.01$). The distribution of significant correlations, the correlation SPM (rSPM), was displayed by rendering the significant pixels onto medial and lateral drawings of each cerebral hemisphere.

RESULTS

The demographic and clinical characteristics of the 40 patients and 23 controls are described in Table 1. The control group were slightly older than the patients (unpaired $t = 2.1$, df 61, $P < 0.04$) but no other significant differences between the groups were found for the demographic variables presented. All patients were moderately to severely depressed according to the 17-item HAM-D.

Factor analysis

The derivation of the 11 collapsed scores considered for entry into the factor analysis is detailed in Table 2. Sampling adequacy was satisfactory for 9 of these scores but 2 (psychoticism and suicidal behaviour) were unsatisfactory and were not included in further analysis. Three factors with eigenvalues greater than 1.0

Table 1. Demographic details of the patients and controls

	Depressed	Controls
Number	40	23
Sex (M/F)	25/15	10/13
Handedness (R/L)	37/3	22/1
Age (mean years $\pm$ S.D.)	56.8 ($\pm$ 12.6)	63.4 ($\pm$ 11.6)
	Range (29–75)	Range (33–77)
HAM-D* (mean $\pm$ S.D.)	25.2 ($\pm$ 4.3)	—
	Range (18–32)	—
MADRS† (mean $\pm$ S.D.)	30.6 ($\pm$ 6.5)	—
	Range (18–44)	—
Education (mean years $\pm$ S.D.)	11.7 ($\pm$ 3.6)	13.1 ($\pm$ 2.6)
Psychotropic medication (+/-)	20/20	—
Unipolar/Bipolar	36/4	—
First episode (+/-)	16/24	—
Length of present episode (mean weeks $\pm$ S.D.)	30 ($\pm$ 32)	—
Number of previous episodes (mean $\pm$ S.D.)	4 ($\pm$ 3.9)	—

* HAM-D indicates the 17-item Hamilton Depression Rating Scale.

† MADRS indicates the Montgomery and Åsberg Depression Rating Scale.

FIG. 1. Statistical parametric maps (t)SPMs showing the location of significant decreases in rCBF in the 40 depressed patients as a group in comparison with the 23 normal controls. Pixels at which there is a significant ($P < 0.001$ non-corrected) decrease in blood flow in the depressed group have been projected onto the medial and lateral cortical surfaces of the left hemisphere.

FIG. 2(a). Correlation SPMs showing those pixels on the cortical surfaces of both cerebral hemispheres at which there is a significant ($P < 0.01$) positive correlation of rCBF with loadings for Factor 1 (psychic and somatic anxiety) in the 40 depressed patients. The white lines indicate the upper and lower limits of the CBF data set used in this analysis.

FIG. 2(b). Correlation SPM showing those pixels on the lateral cortical surface of the left cerebral hemisphere at which there is a significant ($P < 0.01$) negative correlation of rCBF with loadings for Factor 2 (mood/retardation) in the 40 depressed patients. The two parallel white lines indicate the upper and lower limits of the CBF data set used in this analysis.

FIG. 2(c). Correlation SPM showing those pixels on the medial cortical surface of the left cerebral hemisphere at which there is a significant ($P < 0.01$) positive correlation of rCBF with loadings for Factor 3 (cognitive impairment/psychoticism) in the 40 depressed patients. The two parallel white lines indicate the upper and lower limits of the CBF data set used in this analysis.

Table 2. Derivation of collapsed symptom scores. Numbers refer to the coding in SADS-L

Collapsed score	SADS items contributing
Mood	Mood (235), Guilt (241), Self esteem (243), Pessimism (245), Anhedonia (327)
Anxiety	Worry (239), Psychic anxiety (266), Phobic anxiety (268), Hypochondriasis (323), Indecision (324), Concentration (325)
Somatism	Somatic anxiety (264), Energy (316), Appetite (318), Weight loss (319)
Suicidal behaviour	Suicidal thoughts (247), Discrete episodes (248), Intent (249), Lethality (250)
Insomnia	Initial insomnia (273), Middle insomnia (274), Late insomnia (275), Severity (313)
Variability	Reactivity (350), Diurnal variation (351)
Psychoticism	Suspicion (419), Delusions (421), Hallucinations (441)
Cognition	Memory (464), MMSE* total
Activity	Social withdrawal (328), Level of functioning (466)
Retardation	Speech (343), Pausing (344), Monotony (345), Mute (346), Slow (347), Severity (348)
Agitation	Sitting still (335), Pacing (336), Handwringing (337), Picking (338), Shouting (339), Talk (340), Severity (341)

* MMSE: Mini Mental State Examination (maximum score = 30).

Table 3. Loadings for the 9 variables entered into the factor analysis. Variables are grouped according to the size of their loadings for particular factors with a threshold for display of 0.5 in absolute values

	Factor 1	Factor 2	Factor 3
Psychic/Anxiety	0.71		
Somatism	0.72		
Insomnia	0.76		
Agitation	0.69		-0.51
Mood		0.72	
Variability		0.69	
Retardation		0.75	
Activity		0.51	
Cognition			0.90
Eigenvalue	3.4	1.9	1.4
% Variance	30.9	17.6	12.8

accounted for 68% of the group's variance in symptom scores. Table 3 shows the factor matrix after varimax rotation omitting those collapsed scores with a factor loading below 0.5. The first factor identified corresponded to a combination of psychic and somatic anxiety, insomnia and psychomotor agitation. The second factor corresponded to mood and its variability, psychomotor retardation and level of social activity.

Table 4. Omnibus significance for correlations, positive and negative, of rCBF with each of the 3 factor scores. The χ^2 statistic has been used to compare the observed distribution of correlation coefficients with that expected by chance at $P < 0.01$

Factor number	Positive correlations (df = 1)		Negative correlations (df = 1)	
	P	χ^2	P	χ^2
1	< 0.0001	38.4	1	0
2	< 0.0001	30.4	< 0.0001	268
3	< 0.0001	28.5	0.6	0

The third factor corresponded to cognitive performance and psychomotor agitation (inversely related).

Cerebral blood flow

Depressed v. control subjects

Global flow differences A comparison of mean global flow prior to ANCOVA in depressed and control subjects revealed no significant differences (depressed = 27.9 ± 4.5 ml/100 ml/min; controls = 27.2 ± 3.8 ml/100 ml/min; unpaired t tests, $t = 0.64$, $P < 0.53$). Global flow was estimated by averaging all pixels between -8 and +32 mm relative to the intercommissural line without correction for tissue heterogeneity. Subsequent analysis identified regional abnormalities in flow between the two groups after covarying out individual global effects.

Regional differences The comparison of 40 depressed patients with 23 controls identified three areas in the depressed group which showed significantly reduced rCBF. These areas were the left anterior cingulate, the left dorsolateral prefrontal cortex and the left angular gyrus, the areas previously identified in an analysis of 33 subjects (Bench *et al.* 1992) (Fig. 1).

A single region in the depressed patients showed a strong trend towards a significant increase in rCBF ($P < 0.001$ uncorrected). This area was the left posterior cingulate gyrus (BA 23,30).

Medicated v. unmedicated patients

Global flow differences A comparison of mean global flow in medicated and unmedicated depressives revealed no significant differences

(unmedicated = 28.5 ± 5.4 ml/100 ml/min; medicated = 27.2 ± 3.5 ml/100 ml/min; unpaired $t = 0.92$, $P > 0.36$).

Regional differences To determine the possible effects of medication on rCBF a second comparison was made between medicated ($N = 20$) and unmedicated ($N = 20$) depressives. As previously there was no significant change in rCBF at the regions previously identified as having low flow in the depressed group as a whole. A trend to relatively decreased blood flow in the medicated group ($P < 0.001$ uncorrected) was found in the right inferior frontal lobe (BA 47) across three planes from -8 mm to 4 mm.

Relationship between symptom profiles and rCBF

This analysis was directed at exploring the relationships between dimensions of psychopathology and rCBF. The volume analysed was limited to those transverse planes for which there was a complete data set in every subject. Pixels were identified at which there were significant ($P < 0.01$) correlations with each of the factor scores. Each of the three factors showed significant correlations with the profile of rCBF (as assessed by comparing observed and expected numbers of pixels at $P < 0.01$). The omnibus significance for these correlations is shown in Table 4.

Significant positive correlations were seen between the loadings for factor 1 and rCBF in the right posterior cingulate cortex (BA 23) and bilateral inferior parietal lobules (BA 39/40). The correlation SPM for this analysis is shown in Fig. 2a. The most significant correlations for factor 2 were in a negative direction, i.e. increasing factor loading correlating with decreased rCBF. First, an area including the left superior temporal gyrus (BA 22,39) and left inferior parietal lobule (BA 39,40) including the supramarginal and angular gyri (BA 39,40) extending across five planes from $+16$ to $+32$ mm with respect to the AC-PC line was identified. Secondly, strong negative correlations were seen in the left inferior frontal cortex (BA 45,46) from 0 mm to 16 mm relative to the AC-PC line and in the left dorsolateral prefrontal cortex (BA 46,9) from 16 to 32 mm relative to the AC-PC line. The correlation SPM for this analysis is shown in Fig. 2b. Less significant positive correlations (i.e. increasing

loading correlating with increased rCBF) were seen mainly in left-sided structures including the ventral striatum and precuneus, but also in the right inferior temporo-occipital cortex. Significant correlations were also found with factor 3 (higher cognitive performance). Increasing cognitive impairment was associated with decreased blood flow in the left medial prefrontal cortex (BA 10) from -4 to 28 mm, in the right anterior thalamus, the right superior temporal gyrus (BA 22,42), the right postcentral gyrus (BA 40,42) and bilaterally in posterior cingulate cortices (BA 23,31). The rSPM is shown in Fig. 2c.

DISCUSSION

The main focus of this investigation was to relate symptomatic expressions of major depression to underlying cerebral neurophysiology as determined by rCBF. A major obstacle to this approach is the symptomatic heterogeneity of affective disorders which confounds the selection of nosologically pure subgroups of patients. Multivariate analysis has been used to try to establish dimensions of depressive illness within a large sample without an *a priori* categorization (Kendell & Gurlay, 1970; Paykel, 1971). In a group of severely depressed patients, already categorized in terms of satisfying RDC criteria for Major Depression, factor analysis allowed us to reduce a large number of correlated variables (symptom ratings) to a small number of uncorrelated variables (factors). By correlating the factor scores with profiles of rCBF we hoped to identify brain systems subserving the expression of various dimensions of major depressive illness.

The results of our factor analysis are strikingly similar to those previously described by Silfverkiöld *et al.* (1986) in an in-patient sample. In their study of 43 patients with depression referred for ECT and 30 with mania, using $^{133}\text{Xenon}$ inhalation and SPET, a factor analysis produced a factor 5 solution. Diagnostically the depressed patients were more heterogeneous than our sample although the majority fulfilled DSM-III (American Psychiatric Association, 1980) criteria for bipolar disorder depressed or major unipolar depression. The factors produced were: (1) depression-psychomotor retardation; (2) self-depreciation (including suicidal thoughts

and behaviour); (3) anxiety-agitation; (4) cognitive dysfunction; and (5) mania. The limited success in further correlating factor scores with rCBF in the same study most likely reflects the poor topographic resolution of the functional mapping technique used and the limitations of the data analysis methods.

Global blood flow

Our study suggests that there is normal global cerebral blood flow in major depression. This finding is in agreement with some previously reported ^{133}Xe inhalation studies (Johanson *et al.* 1979; Risberg, 1980; Gustafson *et al.* 1981a; Gur *et al.* 1984; Goldstein *et al.* 1985; Silfverskiöld & Risberg, 1989; Delvenne *et al.* 1990) but not others (Mathew *et al.* 1980a, b; Gustafson *et al.* 1981b; Warren *et al.* 1984; Rush *et al.* 1985; Sackeim *et al.* 1987, 1990; Devous, 1989), which found lower global flow values. Some of these studies have examined differences between bipolar and unipolar patients and in general have found no differences attributable to polarity (Uytendenhoeft *et al.* 1983; Delvenne *et al.* 1990; Sackeim *et al.* 1990) although two studies found higher global flows in the bipolar group (Sackeim *et al.* 1987; Silfverskiöld & Risberg, 1989). The two-dimensional methods of CBF estimation with the xenon technique are not directly comparable with PET. In the former, detector response is weighted to the immediately underlying grey matter and the field of view is imprecisely defined. The differential clearance of xenon from grey and white matter enables some assessment of flow from these two tissue compartments. In PET, using a tracer such as H_2^{15}O which has a non-linear response to flow, tomographic slices through the brain volume are produced and measurements, particularly average estimates, are weighted towards low flow tissue compartments (Frackowiak *et al.* 1981). Our measure of global activity includes all elements, neural and non-neural, within the region of interest and is therefore less sensitive to changes in total grey matter blood flow and quantitatively lower than CBF estimated using two-dimensional methods. However, it reflects more accurately the reciprocal changes in flow that occur between cortical and subcortical structures. There are relatively fewer PET studies of affective disorders and results in relation to

global flow and metabolism have been inconsistent, possibly because of the small numbers studied. One group has reported a decrease in whole brain glucose metabolism in bipolar but not unipolar depressives (Schwartz *et al.* 1987). Martinot *et al.* (1990) also found lower cortical metabolism in a group of predominantly bipolar depressives, but small numbers precluded direct examination of the effect of polarity. However, these findings had not been reported in earlier studies of bipolar and unipolar patients (Buchsbaum *et al.* 1984; Cohen *et al.* 1989). A recent PET study using H_2^{15}O to measure CBF found no difference in global flow between unipolar patients in the depressed or euthymic state and normal controls (Drevets *et al.* 1989). Our findings regarding global flow are therefore consistent with previous PET studies of unipolar depressives. Our sample only included four bipolar patients and therefore examination of the effect of polarity is not possible.

Regional changes

The present study suggests that regional neurophysiological disturbances in patients with major affective disorders are multifocal, involving association and paralimbic cortices. The findings, which are in accordance with an earlier report (Bench *et al.* 1992), can be interpreted as indicating that major depression is an expression of pathophysiological deficits in widely distributed, though functionally and neuroanatomically connected, neuronal networks. The evidence from this study also implies that specific clinical components of the depressive syndrome are associated with discrete areas of regional cerebral dysfunction. Specifically, increased blood flow in the posterior cingulate cortex and inferior parietal lobule correlates with increased loading on a score for a clinical dimension of psychomotor agitation. Decreased rCBF in the left DLPFC and the left angular gyrus is highly correlated with a dimension of psychomotor retardation and mood disturbance. In the left anterior medial prefrontal cortex, an area previously identified as functionally abnormal in a categorical comparison of a smaller group of cognitively impaired depressed patients (Dolan *et al.* 1992a), decreased rCBF is correlated with increasing cognitive impairment. The strong correlations between patterns of rCBF deficits and both clinical and neuropsychological

measures suggest that functional specificity can be attributed to regional neurophysiological deficits in functional psychiatric disorders.

While the present study implicates multiple areas as functioning abnormally the greatest credence can be given to those areas identified in both the categorical and dimensional analyses. The finding that decreased perfusion in the DLPFC relates to a clinical picture of psychomotor retardation and mood disturbance is of considerable theoretical interest. Critical components of psychomotor retardation include diminished spontaneous speech and a general impoverishment of verbal expression. Such features are key elements in the language disturbances described in patients with lesions in these and adjoining areas, often referred to as 'central motor aphasia' (Goldstein, 1948) or 'frontal dynamic aphasia' (Luria, 1970). In a study of patients with chronic schizophrenia, using an identical data analytic methodology to that described in the present study, decreased rCBF in the left DLPFC was found to be significantly related to a clinical picture of psychomotor poverty (Liddle *et al.* 1992). The relevance of this finding is the considerable overlap in the symptom pattern of this syndrome and that of psychomotor retardation in depression. Furthermore, the relationship of psychomotor impairment with decreased rCBF in this brain region has been shown to be independent of mood disturbance (Dolan *et al.* 1992*b*). Therefore, two diagnostic entities – depression and schizophrenia – with similar behavioural expressions, display a common regional neurophysiological deficit.

Psychomotor poverty and retardation can be characterized in neuropsychological terms as conditions in which there is an impoverishment of intentional behaviour. The presence of a regionally specific functional deficit across two syndromes where there is an impairment in intentional set predicts that this cortical region is critical in the expression of such behaviours. This implies a three-way link between abnormal DLPFC function, psychomotor retardation and the normal functional anatomy of the DLPFC. Strong support for such a three-way link comes from PET activation studies in normal control subjects which have investigated the brain areas involved in intrinsically generated behaviour. In two separate studies, using a verbal fluency

paradigm and a motor generation task, the common region of activation was centred on the left DLPFC (Frith *et al.* 1991).

Lesion studies in primates have illuminated the role of the DLPFC in neuropsychological function. The DLPFC does not appear to contribute to attentional aspects of behaviour and surprisingly such lesions in non-human primates statistically improve performance on sensory discrimination tasks (Irlé, 1990). The DLPFC has been specifically associated with response selection in the absence of extrinsic information (Goldman-Rakic, 1986). This is a definition of intrinsically generated, volitional, willed or intentional behaviour. However, the functions of such a large area of the neocortex as the DLPFC are unlikely to be restricted to the generation of intrinsic behaviours, particularly in the light of the massive connectivity of this area with other cortical and subcortical regions. This region is likely to subserve multiple parallel functions and, as for other cortical regions, these functions are defined in terms of external connectivity (Edelman & Mountcastle, 1977). In other words the neuropsychological functions of the prefrontal cortex are best conceptualized with reference to its connections with other structures (Goldman-Rakic, 1988).

Significant correlations with psychomotor retardation and mood were also observed in the left angular gyrus. Decreased rCBF in a similar cortical region has been described previously in an investigation of depressed subjects using the xenon inhalation technique (Sackeim *et al.* 1990). In the present study this area, in association with the DLPFC, was highly correlated with a clinical picture of psychomotor retardation. These cortical regions have likewise been implicated in a psychomotor poverty syndrome of schizophrenia (Liddle *et al.* 1992). The functions of the angular gyrus are multimodal, although data from lesion studies in primates and human clinical studies imply a role in visuospatial orientation and attention, in particular to stimuli that are of significance to the organism (Heilman *et al.* 1970; Mountcastle & Lynch, 1975; Lynch, 1980; Mesulam, 1983). Although we take the view that psychomotor retardation is characterized neuropsychologically by impoverishment of self-generated behaviours, a striking aspect of the syndrome is the absence of emotional response to environmental stimuli.

A strong positive correlation was observed between increased blood flow in the posterior cingulate and inferior parietal lobules and increasing psychomotor anxiety and agitation. Anxiety is invariably seen in depressive illness and this analysis suggests that the posterior cingulate, in concert with the inferior parietal cortex, may contribute this symptom cluster to a distributed system involved in the manifestation of emotional disorders. This finding is particularly interesting in the context of our associated finding of decreased rCBF in the anterior cingulate in depressed patients. Reciprocal anatomical connections are well described between the anterior and posterior cingulate and the demonstration in this study of a relative increase in rCBF in the posterior cingulate in association with a decrease in the anterior cingulate supports the notion of functional coupling (Baleydier & Mauguière, 1980).

The cingulate cortex has long been implicated in the regulation of affect (Papez, 1937) and a role for this area in pain perception has been established both on the basis of the effects of surgical ablation (Foltz & White, 1962) and functional imaging studies (Jones *et al.* 1991; Talbot *et al.* 1991). Attentional aspects of behaviour have also been attributed to this cortical area (Pardo *et al.* 1990; Posner & Petersen, 1990). The neuroanatomical connectivity of the anterior cingulate, involving higher association and limbic connections, is consistent with a role in the mediation of motivational and emotional states (Mesulam, 1983). Its precise role in the regulation of affect is not easy to define although recent theories imply that it imbues behavioural tone to higher-order experiences (Mesulam, 1986). Such formulations are consistent with findings, in monkeys, that the cingulate cortex is critical in the attribution of emotional significance to sensory stimuli (Gabriel *et al.* 1982). These considerations make it surprising that no correlation emerged between any of the symptom factors, in particular the psychomotor/mood factor, and decreased perfusion in the anterior cingulate. A likely explanation may well be that as all our patients were in the moderate to severe end of the spectrum of depression the variance in rCBF across subjects in this region was minimal. In other words regional dysfunction in this area was common to all our patients while other

areas of regional dysfunction were related to specific dimensions of illness.

We have previously described a decrease in rCBF in the medial prefrontal cortex in patients with 'depressive pseudodementia' (Dolan *et al.* 1992a). This finding, from a direct categorical comparison of depressed patients with and without cognitive impairment, receives strong support from the present findings of a significant correlation between impaired cognition and decreased rCBF in the medial prefrontal pole. The dimensional analysis has arguably greater validity in that impaired cognition, to a greater or lesser degree, is invariably part of the clinical picture of affective illness. Although no specific neuropsychological function has been attributed to the anterior medial prefrontal cortex this region is characterized neuroanatomically by reciprocal connections with higher-order association areas, particularly the dorsolateral and caudal orbitomedial prefrontal cortex, as well as the anterior cingulate cortex (Kendell & Gourlay, 1970). Thus, its connectivity is consistent with a role in higher-order cognition. A PET study of patients with chronic alcohol dependence has described a decrease in glucose metabolism in a similar region, with the decrease being correlated with neuropsychological impairment (Gilman *et al.* 1990). Deficits in this region may therefore be critical in the cognitive impairments seen in functional psychiatric disorders.

From an anatomical perspective, the importance of the focal abnormalities described in the present investigation of depression is highlighted by primate studies which indicate patterns of reciprocal neuroanatomical connectivity between the DLPFC, the anterior cingulate cortex, and the angular gyrus. The DLPFC, the cingulate cortex and the medial frontal cortex also share a pattern of mutual connectivity (Pandya *et al.* 1981). The prefrontal areas in particular are sites of convergence for both limbic inputs with highly processed associative information and this pattern of connectivity is thought to mediate the integration of thought and emotion (Mesulam, 1986).

The decreases in rCBF described are lateralized to the left cerebral hemisphere. These findings are at variance with views that depressive disorders are more closely related to right hemisphere dysfunction (Flor-Henry, 1979)

but are in keeping with more recent views of hemispheric function in depression (Cutting, 1992) and in particular other PET findings (Mathew *et al.* 1980a; Baxter *et al.* 1989; Martinot *et al.* 1990). The results are also consistent with some (Robinson *et al.* 1983, 1984) but not all (House *et al.* 1990; Sharpe *et al.* 1990) lesion studies of patients with cerebrovascular accidents where both left-sidedness and proximity to the anterior frontal pole have been associated with an increased likelihood of depression.

We do not yet know whether the regional abnormalities we have described are state or trait dependent. Only a minority of functional imaging studies have examined patients longitudinally, in different clinical states. A study of patients before and after ECT using xenon inhalation showed a post-treatment decrease in global blood flow (Silfverskiöld & Risberg, 1989) and longer-term effects have been reported that suggest that clinical response to ECT is associated with a further lowering of global flow (Sackeim *et al.* 1990). In contrast, relative hypometabolism in the left dorsolateral prefrontal cortex identified using PET has been shown to normalize with treatment for depression (Baxter *et al.* 1989), whereas others have shown disappearance of left-right asymmetry but persisting relative hypofrontality and whole cortex hypometabolism (Martinot *et al.* 1990). In order to evaluate whether the regional and global abnormalities described are related to state or trait factors long-term follow-up of patients with repeat examinations is necessary.

The neurophysiological deficits identified in the present study cannot in any sense be considered as causative. Regional dysfunction might reflect abnormalities of neurotransmitter input; the sites identified in the present study receive inputs from all of the brainstem monoaminergic systems. The direct exploration of putative dysfunction of specific neurotransmitter systems in depression is an important goal of future research. Among the neurotransmitter systems that may have a role in the pathogenesis of affective disorders, dopamine concentrations exhibit the greatest degree of cortical topographical specificity, being particularly high in the prefrontal cortex compared to other cortical sites (Brown *et al.* 1979). Dopamine has also been implicated in aspects of higher-order

cognition, particularly those subserved by the prefrontal cortex (Brozoski *et al.* 1979; Sawaguchi & Goldman-Rakic, 1991).

The determination of the neuromodulatory role of monoaminergic neurotransmitter inputs, specifically in relation to neuropsychological function, constitutes an important research strategy. Such strategies have recently been described using the xenon inhalation technique (Weinberger *et al.* 1988) and PET (Friston *et al.* 1991c). These approaches, involving conjoint neuropsychological and neuropharmacological manipulations, should extend the framework for understanding the mechanisms involved in major psychiatric disorders through the formulation of neurotransmitter deficits in terms of their functional specificity.

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