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Changes in regional cerebral blood flow on recovery from depression

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SYNOPSIS We have previously described focal abnormalities of regional cerebral blood flow (rCBF) in the left dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex and angular gyrus in 40 patients with major depression. We now report on the patterns of change in rCBF in a subgroup of 25 of the same patients who were rescanned following clinical remission of depression. Fifteen patients were scanned when optimally matched for drug treatment (4) or drug free on both occasions (11). The other 10 patients were fully recovered but could not be matched for drug status for clinical and ethical reasons. In a paired comparison of the same patients when ill and following recovery it was evident that remission was associated with a significant increase in rCBF in the left DLPFC and medial prefrontal cortex including anterior cingulate. Increases in rCBF in the angular gyrus were not seen when the comparison of depressed and recovered scans was matched for medication. The previously described relationship between clinical symptoms and brain perfusion in the depressed state was no longer present in the recovered state; this supports the hypothesis of state relatedness. Thus, recovery from depression is associated with increases in rCBF in the same areas in which focal decreases in rCBF are described in the depressed state in comparison with normal controls.

INTRODUCTION

The view that affective illness has a relatively good prognosis is primarily based on the Kraepelinian notion that manic-depressive disorder is a remitting illness (Kraepelin, 1921). Empirical research has, however, demonstrated that affective illness follows a recurrent, episodic course in a majority of individuals (Keller *et al.* 1982). Between 50 and 85% of patients with a major depressive disorder will have at least one subsequent episode of depression in their lifetime (Consensus Development Panel, 1985). Long-term follow-up studies have shown that depression is also associated with a significant chronic morbidity (Coryell & Winokur, 1982). A 20-year outcome study of depression found that less than one-fifth of survivors remained well, with over one-third of the series having an unnatural death or severe chronic distress and handicap (Lee & Murray, 1988). Other studies conducted over similar timescales concur with these findings (Coryell *et al.* 1990; Maj *et al.* 1992). Recurrent depression is thus a major public health issue, particularly in view of the evidence that its incidence has increased dramatically over the last 30 years (Jablensky, 1987).

There is compelling evidence for a biological basis to major affective disorders (Rush *et al.* 1991). In addition to genetic predisposition (Allen, 1976; Bertelsen *et al.* 1977), there are well described neurochemical, neuroendocrine, neuropsychological and sleep abnormalities (Miller, 1975; Meltzer, 1987; Reynolds & Kupfer, 1987; Cowen, 1991). A critical issue concerning such biological abnormalities is whether they represent state markers, present only when the patient is depressed, or trait abnormalities that endure even with clinical recovery. The most promising trait markers are abnormalities in REM sleep (Reynolds & Kupfer, 1987), in cation transport mechanisms (Wood *et al.* 1991) and in indices of central noradrenergic neurotransmission (Katona *et al.* 1987). On the other hand, the blunted neuro-

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endocrine response to L-tryptophan appears to be a reliable state marker (Cowen & Anderson, 1991).

Functional brain imaging provides a direct means of assessing central neural activity. In depression, studies have primarily involved either cross-sectional comparisons with controls or correlations of cerebral blood flow or metabolism with clinical variables. Both global (Mathew *et al.* 1980; Baxter *et al.* 1985; Kanaya & Yonekawa, 1990; Sackeim *et al.* 1990) and regional (Buchsbaum *et al.* 1984; Post *et al.* 1987; Baxter *et al.* 1989; Kanaya & Yonekawa, 1990; Martinot *et al.* 1990; Sackeim *et al.* 1990; Austin *et al.* 1992*a*) decreases in cerebral blood flow and metabolism have been described during the depressed state. Exceptions to these findings include studies which have described increases in frontal areas (Uytedenhoef *et al.* 1983; Reischies *et al.* 1989; Silfverskiold & Risberg, 1989; Drevets *et al.* 1992; Wu *et al.* 1992). The contradiction across some studies may represent differences in patient selection criteria such as family history for depression (Drevets *et al.* 1992), response to sleep deprivation therapy (Wu *et al.* 1992) or referral for ECT (Johanson *et al.* 1979; Silfverskiold & Risberg, 1989; Sackeim *et al.* 1990).

Only a minority of studies have examined patients both in the illness phase and in the recovered state. Hurwitz *et al.* (1989) found no differences in rCBF in patients after 5–7 weeks of imipramine treatment whereas Kanaya *et al.* (1990) found a trend for cortical rCBF to increase to normal values after treatment. Wu *et al.* (1992) reported a decrease in cingulate and amygdala metabolism post-treatment in a subgroup of patients who responded to sleep deprivation. Drevets & Raichle (1992) found that in 3 patients followed longitudinally, decreased activity in the DLPFC and a non-significant increase in left caudate activity coincided with clinical recovery. Other studies have described a relative normalization of left DLPFC glucose metabolism on recovery (Baxter *et al.* 1989; Martinot *et al.* 1990). A limitation of these studies is the difficulty in interpretation of findings based upon small sample sizes and differing medication status between pre- and post-treatment assessments.

We have previously reported focal deficits in rCBF, affecting the left anterior cingulate, dorsolateral prefrontal cortex and the left angular gyrus in a cohort of 40 depressed patients who met Research Diagnostic Criteria (RDC) for major depression (Bench *et al.* 1993*a*). In this study regional abnormalities were significantly related to symptom profile scores. The aim of the present study was to examine the profile of changes in brain activity with clinical recovery. Our specific hypothesis was that there would be state related increases in brain activity (as indexed by rCBF) in those areas where we previously identified decreased activity in the depressed state.

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 severity of depression was assessed with the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). Three of the 40 patients had a bipolar illness. 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 was recruited. The details of these patients have been published previously (Bench *et al.* 1993*a*). All the 40 patients initially recruited were followed

closely over the course of the study and 29 of these patients recovered clinically. Many of them were seen on a regular basis by two of the authors (C.J.B. or R.J.D.) and the condition of the others was established by regular contact with the responsible clinical teams and telephone or written correspondence with the patients. For patients where there was clinical evidence of recovery a follow-up assessment was made. Following this assessment a second assessment was made between 4 and 6 weeks later. The definition of recovery was made with reference to the criteria described by Frank *et al.* (1991). Recovery was considered to have occurred if at the second assessment the patients had less than two symptoms present according to the Schedule for Schizophrenia and Affective Disorders for more than 8 weeks. These patients were re-scanned in the recovered state, wherever possible with the same medication status as when first scanned. For those patients who had been unmedicated at the index assessment this required a withdrawal from medication after a period of recovery, as previously defined, when this was considered clinically and ethically possible. The normal control group was made up of 23 unpaid normal volunteers whose characteristics are described elsewhere (Bench *et al.* 1992). None of the controls had a history of neurological or psychiatric illness, neither were they taking psychotropic medication at the time of scanning. Follow-up data were not available on 15 of the patients. 8 remained chronically ill, 4 refused, 2 were lost to follow up and one committed suicide. Ethical approval for the study 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.

PET methods

The PET methodology has been described in detail in a previous publication (Bench *et al.* 1992). Regional cerebral blood flow was measured under resting conditions using the CTI model 931-08/12 PET scanner (Spinks *et al.* 1988). ^{15}Oxygen 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 22G catheter at 0, 5 and 10 min into the acquisition period. A Hanning filter with a cut-off frequency of 0·5 Hz 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 up to May 1992.

Image analysis

The blood flow images were analysed using Statistical Parametric Mapping (SPM) software as previously described (Friston *et al.* 1991*a*; Friston & Frackowiak, 1991). This technique allows pixel by pixel analysis of functional images with the end result being a statistical parametric map (SPM). For this map each pixel value represents a statistical quotient, in the case a *t* value. The first stage in this analysis involves stereotaxic normalization of the images to a standard template using both linear rescaling (for size) and non-linear resampling of data (for shape) (Friston *et al.* 1991*b*). The image volume is then resliced into a standard brain volume (Talairach & Tournoux, 1988) with an inter-planar distance of 4 mm, a pixel size of 2×2 mm and the reference (AC–PC) plane at 0 mm.

Transformation of images from different subjects into a standard stereotaxic space attempts to minimize variance due to brain shape, size and position. When the same subject is scanned on two occasions, in this study in the depressed and recovered state, the variability of head position in the scanner will account for the greatest portion of this variance. Therefore, prior to stereotaxy and subsequent statistical analysis, the scans from patients in the depressed and recovered state were co-registered in the following manner. For each patient, the two scans (depressed and recovered) were processed using automatic image realignment (AIR) software to minimize the effects of variability in head position between scans (Woods *et al.* 1992). In this procedure anatomical information from the brain images themselves is used to calculate the linear and angular displacements

Table 1. *Demographic details of the subjects studied*

	Depressed	Recovered	Controls
Number	25	25 TC123	
Sex (m/f)	14/11		10/13
Age	58·6 (±12·6)		63·4 (±11·6)
Years Ed.	11·8 (±3·9)		13·3 (±2·6)
HAM-D*	23·9 (±4·2)	7·6 (±5·1)	
MADRS†	29·2 (±5·8)	8·9 (±5·2)	
MMSE‡	24·6 (±5·0)	25·6 (±4·2)	

* 17-item Hamilton depression rating scale.
† Montgomery and Åsberg rating scale.
‡ Mini-Mental State Examination.

necessary to align the images to a reference image, in this case the index (depressed) scan. The alignment algorithm calculates the ratio of one image to another at each voxel in the brain and then align the two images such that the variance of this ratio across all voxels is minimized.

Categorical comparisons of rCBF images

In the statistical analysis three separate comparisons were performed: (1) depressed patients *v.* normal controls (unpaired); (2) recovered patients *v.* depressed patients (paired); and (3) comparison of recovered and depressed patients optimally matched for medication status (paired). For each categorical comparison (paired or unpaired) the stereotactically normalized CBF images were adjusted so as to remove individual differences in global blood flow using an analysis of covariance (ANCOVA) (Friston *et al.* 1990). This procedure generates an adjusted mean blood flow map for each group (i.e. depressed, recovered and controls) and an estimate of the error variance for the rCBF at each pixel location for each group. SPM software does not allow an analysis of variance of adjusted rCBF between three groups of unequal size and so individual comparisons between the groups were made using the t statistic. For the paired comparison of depressed and recovered state scans a paired ANCOVA and t test was used to sensitize the statistic. This analysis was done for each pixel and the resulting set of t values constituted the t-statistical map (SPM{t}). For the paired comparisons a statistical threshold of $P < 0{\cdot}001$ was used. This threshold has been shown empirically to detect 5% changes in focal activity without false positives (Bailey *et al.* 1991). In the comparison of the 25 depressed patients with the normal controls we specifically predicted focal decreases in rCBF with the same topographic distribution as previously described in the full cohort of 40 but with a lower level of significance in view of the smaller numbers. For this reason the threshold for this comparison was set at $P < 0{\cdot}01$.

RESULTS

(A) Clinical/demographic data

In demographic terms the 25 patients who were successfully followed up were representative of the original cohort of 40 patients. The remaining 15 patients were slightly more depressed at index assessment: HAM-D = 23·9, S.D. 4·3 ($N = 25$) *v.* 27·3, S.D. 3·5 ($N = 15$); ($t = 2{\cdot}63$, $P < 0{\cdot}01$). There was no difference in the level of cognitive function at initial assessment in the depressed state as indexed by scores on the Mini-Mental State Examination (MMSE) in the 25 patients followed up compared with the remaining 15 patients: MMSE = 24·6, S.D. 5·0 ($N = 25$) *v.* 26·7, S.D. 3·5 ($N = 15$); ($t = 1{\cdot}47$, $P < 0{\cdot}15$).

The demographic and clinical characteristics of the 25 patients in the longitudinal study and 23 controls are described in Table 1. There were no significant differences between these groups for the demographic variables presented. The average time between scans for the patients was 43 weeks (range 13–132 weeks). The mean scores of the patients at index assessment for the 17-item HAM-D and MADRS were 23·9 and 29·2 respectively, indicative of moderate to severe depression. After clinical recovery the scores on these scales reduced as expected. Scores on the MMSE increased significantly from the depressed to the recovered state (paired $t = 2{\cdot}2$, df = 24, $P < 0{\cdot}04$). Patients who were followed up were also divided into those studied under well-matched (for medication) conditions ($N = 15$; 11 drug-free, 4 on identical drugs and drug dosage before and after recovery) and those who were not ($N = 10$). The number of males to females in the matched sample was 9 to 6 and in the unmatched sample was 7 to 5. These two groups were not distinguishable by other clinical variables.

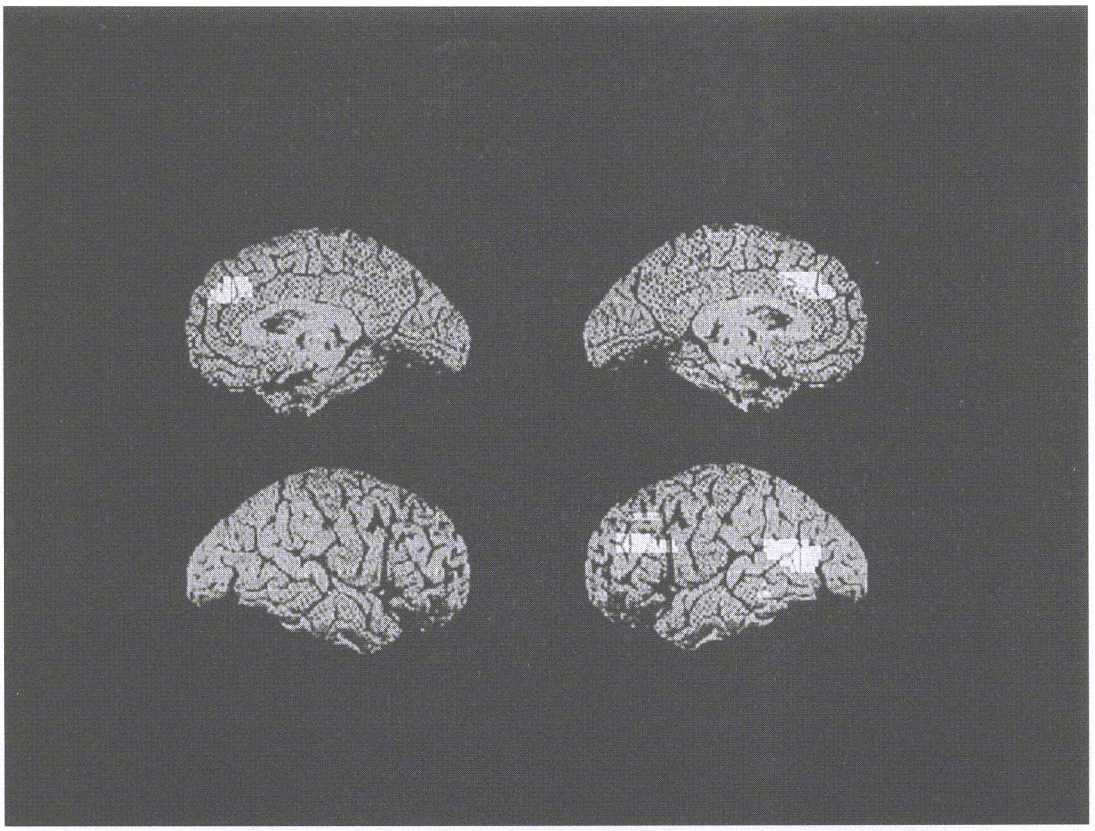

FIG. 1. Statistical parametric map (*t*)SPM showing the location of significant decreases in blood flow in the 25 depressed patients as a group compared with 23 normal controls. Pixels at which there is a significant ($P < 0{\cdot}01$) decrease in blood flow in the depressed group have been projected onto the medial and lateral cortical surfaces of both hemispheres.

Table 2. *The significance and size of the changes in rCBF in the three groups studied, depressed, recovered and normal controls in the three key areas originally identified as having decreased rCBF in the cohort of* 40 *depressed patients when compared with normal controls*

(The *Z* score is a measure of the degree of significance of the difference and is 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. This measure takes into account both the size of the change in blood flow and the variance in each group. ΔrCBF is the change in rCBF equivalent values (normalized to a global rCBF of 50 ml/dl/min) between the two groups in ml/dl/min. These changes in rCBF equivalents are also expressed as percentages.)

Comparison	Threshold *P*	Medial prefrontal/ anterior cingulate			Left DLPFC			Angular gyrus		
		Max *Z*	ΔrCBF	%	Max *Z*	ΔrCBF	%	Max *Z*	ΔrCBF	%
DEP40 *v.* NC	< 0·001	3·6	↓2·8	4·8	3·9	↓2·5	4·9	3·8	↓2·8	5·2
DEP25 *v.* NC	< 0·01	2·9	↓2·9	5·1	2·8	↓2·2	4·6	3·3	↓3·4	6·1
DEP25 *v.* REC25	< 0·001	3·6	↑2·7	5·4	3·74	↑2·2	4·1	3·5	↑2·0	4·1
DEP15 *v.* REC15	< 0·001	3·5	↑3·3	6·2	3·9	↑3·7	7·2			

DEP40, original cohort of 40 depressed patients.
DEP25, 25 patients who were successfully followed longitudinally, in the depressed state.
REC25, 25 patients who were successfully followed longitudinally, in the recovered state.
NC, 23 normal controls.

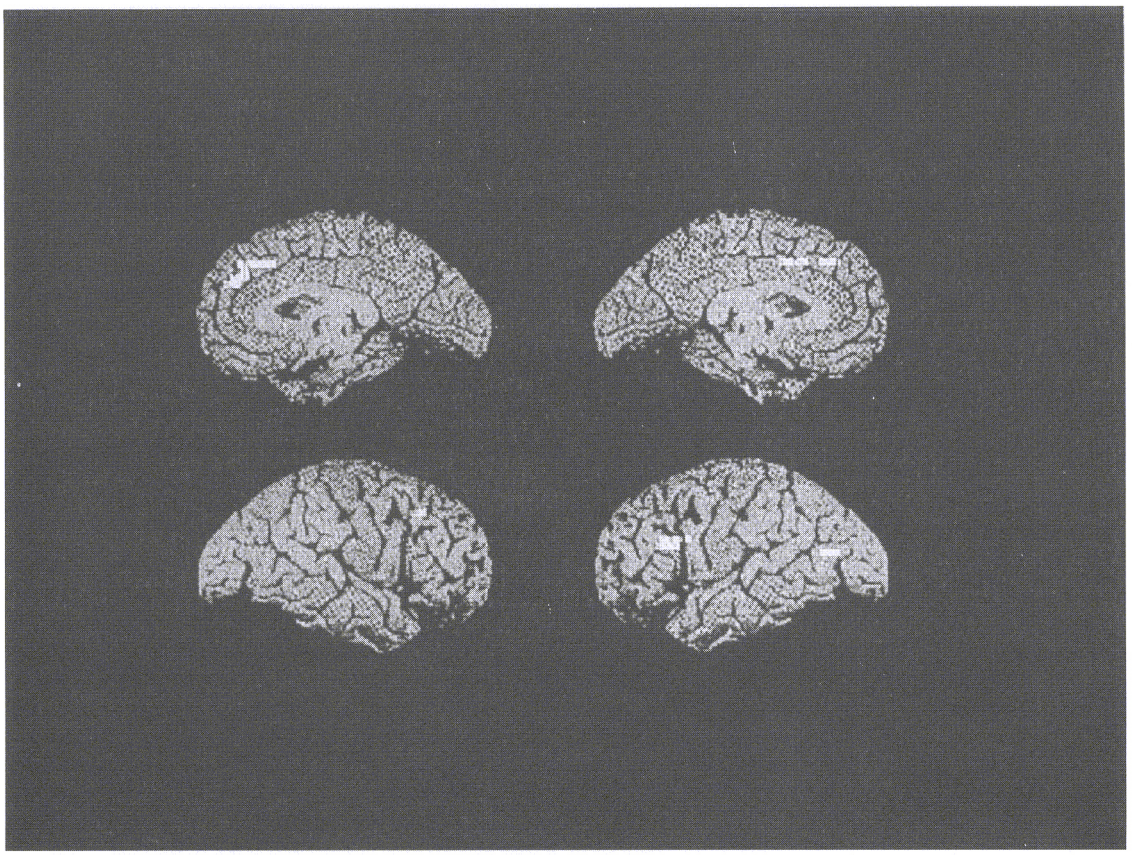

FIG. 2. Statistical parametric map showing the location of significant increases in blood flow in the 25 recovered patients as a group compared with the scans from the same patients in the depressed state. Pixels at which thee is a significant ($P < 0{\cdot}001$) increase in blood flow in the recovered group have been projected onto the medial and lateral cortical surfaces of both hemispheres.

(B) Cerebral blood flow

(*1*) *Depressed* v. *control subjects* (*unpaired*)

A comparison of mean global flow prior to ANCOVA in depressed and control subjects revealed no significant differences. The comparison of 25 depressed patients with 23 controls showed significant decreases in blood flow in the depressed group at the $P < 0{\cdot}01$ threshold localized to the left and right medial prefrontal cortex including the pregenual region of the anterior cingulate cortex, the left lateral prefrontal cortex, and the left posterior parietal cortex including the inferior parietal lobule and the angular gyrus confluent with the posterior aspect of the superior temporal sulcus. These areas were previously identified in the analysis of the full cohort of 40 depressed subjects (Bench *et al.* 1993*a*). These results confirm that the subgroup of 25 patients followed longitudinally are representative in terms of rCBF abnormalities of the initial cohort of 40. The distribution of these decreases is shown in Fig. 1. The size and significance of the changes in rCBF in individual regions is given in Table 2.

(*2*) *Depressed* v. *recovered patients* (*paired*)

A comparison of mean global flow prior to ANCOVA in recovered and depressed subjects revealed no significant differences. The paired comparison of the scans from the 25 recovered patients with the 25 scans from the same patients acquired in the depressed state showed that there were highly significant increases in blood flow in the recovered group at the $P < 0{\cdot}001$ threshold, localized to the left DLPFC, and the

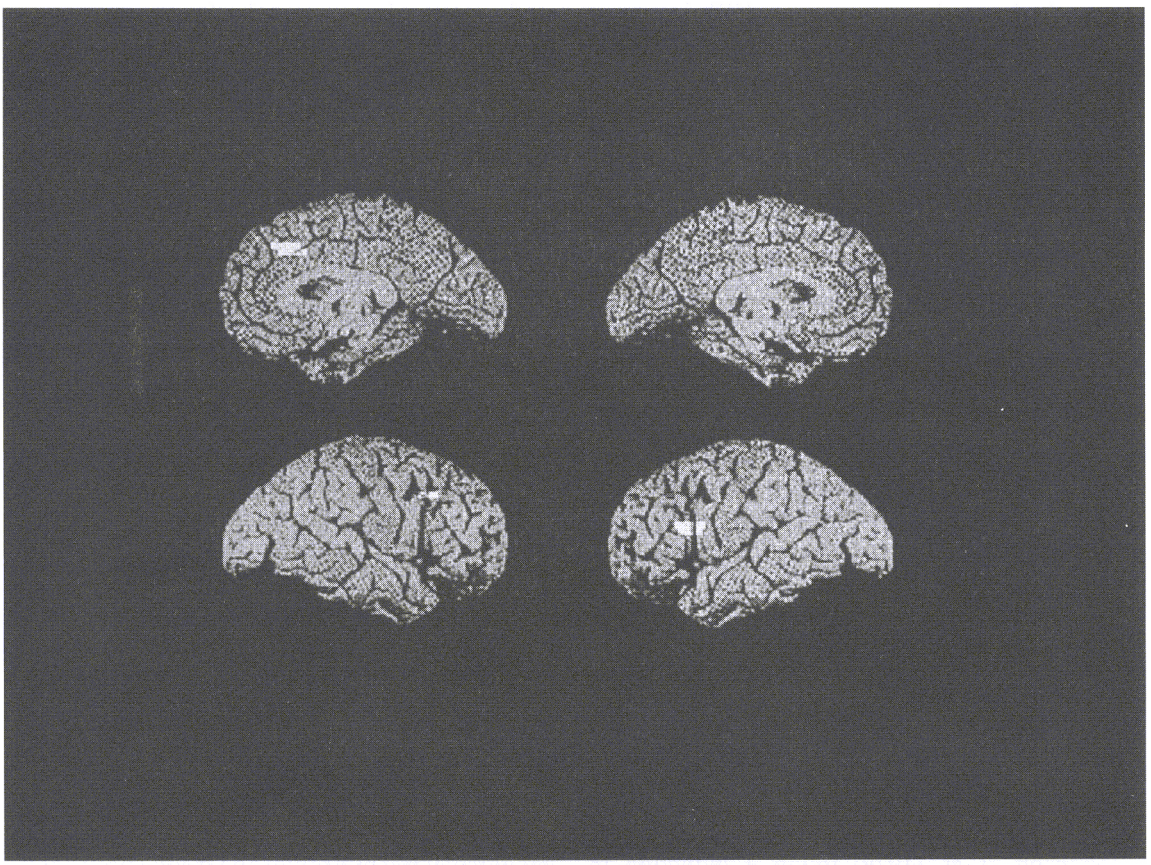

FIG. 3. Statistical parametric map showing the location of significant increases in blood flow in the 15 recovered patients optimally matched for medication compared with the scans from the same patients acquired in the depressed state. Pixels at which there is a significant ($P < 0{\cdot}001$) increase in blood flow in the recovered group have been projected onto the medial and lateral cortical surfaces of both hemispheres.

medial prefrontal cortices bilaterally including the high anterior cingulate cortex (BA 32) and in a region of the posterior parietal cortex posterior to the angular gyrus (Fig. 2). The size and significance of the changes in rCBF in individual regions is given in Table 2.

(*3*) *Depressed* v. *recovered patients, optimally matched for medication status* (*paired*)

For the sample of optimally matched (as previously defined, $N = 15$) patients, a comparison of mean global flow prior to ANCOVA in recovered and depressed subjects revealed no significant differences. The paired comparison of the scans from the 15 recovered patients with the 15 scans acquired in the depressed state showed that there were significant increases in blood flow in the recovered group at the $P < 0{\cdot}001$ threshold, localized to the left dorsolateral prefrontal cortex and the medial prefrontal cortices including the pregenual region of the anterior cingulate cortex on the right (Fig. 3). No increases in rCBF in the region of the angular gyrus were seen at this level of significance. The size and significance of the changes in rCBF in individual regions is given in Table 2.

DISCUSSION

Summary of findings

The main aim of this investigation was to examine the profile of changes in brain activity associated with recovery from depression and specifically to establish whether these overlapped

with the focal abnormalities of rCBF identified in the depressed state. The findings confirm that there are highly significant increases in rCBF from the depressed to the recovered state, most significantly in the left lateral and medial prefrontal cortices. Thus, the brain regions showing the most significant change with clinical recovery from depression are those previously shown to be functionally abnormal in the depressed state. The pattern of increased function in these areas with clinical recovery, as indexed by increasing blood flow, suggests that such changes represent state abnormalities.

Previous studies

Although functional imaging studies of depressed patients often produce conflicting results there is converging evidence for abnormalities of cerebral blood flow and metabolism in anterior and paralimbic brain regions. However, few studies have reported on patients studied before and after clinical recovery. The reported findings in the literature have seldom been convincing due to small patient numbers and the possible confounding effects of continuing medication. Furthermore, results are difficult to compare across studies in view of differences in methodology and patient selection.

Using the Xenon 133 inhalation technique Johanson *et al.* (1979) found a reduction in mean hemispheric CBF of about 10% in 19 depressed patients after ECT. A similar post-ECT decrease in global blood flow was reported by Silfverskiold & Risberg (1989). A preliminary report suggests that clinical response to ECT is associated with a further lowering of global flow (Sackeim *et al.* 1990). Reischies *et al.* (1989) found a decrease in rCBF of the left prefrontal cortex after remission and treatment with antidepressants. Using PET and ^{18}FDG to measure cerebral glucose metabolism (CMRGlu), Buchsbaum *et al.* (1984) found relative 'hypofrontality' i.e. a diminished anteroposterior gradient in depressed patients. Using a similar technique Baxter *et al.* (1985) reported that the whole brain metabolic rate for bipolar depressed patients increased on recovery from depression to the euthymic or manic state, with or without medication. In addition, unipolar depressed patients, rescanned on recovery, showed increase of the mean caudate:hemisphere ratio (Baxter *et al.* 1985). In a further study, relative hypometabolism in the left dorsolateral prefrontal cortex of 12 unmedicated depressed patients showed a significant increase in the left DLPFC: hemispheric metabolic ration on recovery. Although these latter findings suggest that relative DLPFC hypometabolism is a state marker for major depression, they are difficult to interpret since none of the patients were matched for medication status in the depressed and recovered states (Baxter *et al.* 1989). Consistent with these findings are those of Martinot *et al.* (1990) also using PET and ^{18}FDG, who found that relative hypometabolism in the left DLPFC in the depressed state, disappeared with treatment. This again suggests that relative normalization of left-sided prefrontal dysfunction relates to clinical improvement.

Contradictory findings, wherein changes in function with clinical recovery have been associated with decreases in rCBF or rCMRGlu have also been reported. Wu *et al.* (1992) reported that increased CMRGlu in the cingulate and amygdala in depressed patients predicted response to total sleep deprivation (TSD). Responders had a significant decrease in their initially high CMRGlu in the cingulate after TSD. Using PET and ^{15}Oxygen, Drevets *et al.* (1992) reported increased blood flow in the left dorsolateral prefrontal and medial prefrontal cortices and amygdala, and decreased flow in the left caudate in a group of unmedicated unipolar depressed patients selected specifically by their family history of major depressive illness. A subgroup of 3 patients rescanned on remission after an interval of 8 weeks, and following treatment with desipramine, had a decrease in rCBF in the left prefrontal cortex (Drevets & Raichle, 1992). The authors suggested that the susceptibility to depression in these highly selected patients is manifested as a trait marker of increased rCBF in the left amygdala whereas the changes in the left prefrontal cortex represent a state abnormality.

Methodological issues

Measurements made by tomographic functional imaging techniques are potentially confounded in brains with reduced tissue mass. In depressed patients there is evidence of increased ventricular brain ratios and cerebral atrophy, and diminished caudate nucleus volume, particularly in

older patients (Dolan *et al.* 1985, 1986; Krishnan *et al.* 1992). Most studies have found that these changes are generalized, unrelated to clinical features of depression, and are non-progressive. A more recent study by Coffey *et al.* (1993) in an elderly group of depressed patients referred for ECT found reductions of around 7% in frontal lobe volume. However, the methodology did not allow differential estimation of grey and white matter volume nor subregional measures within the frontal lobes. The majority of the metabolic abnormalities identified by PET in atrophic brains cannot be explained by cortical atrophy alone (Fazekas *et al.* 1989). In theory however, a direct comparison of composite PET images from groups of different subjects may produce artefactual results if there are systematic differences in anatomy that are not fully compensated for by stereotaxic transformation. Particular difficulties may be encountered when comparing psychiatric groups with a control group (Smith *et al.* 1988). The likelihood of such errors is reduced by employing image averaging with relatively low-resolution images from several subjects. One of the aims of the present study was to overcome some of these difficulties by using a test–retest design, and image processing which minimizes the effect of positional differences at the time of scanning (Woods *et al.* 1992). In the case of the present study the time scale of follow-up is unlikely to be associated with important structural change though there is an inherent order effect in our study in that patients were always scanned in the depressed state first.

A further important consideration is the contribution of medication effects. We previously reported that depressed patients on a variety of medications had relatively decreased rCBF in the right inferior frontal lobe compared with non-medicated patients (Bench *et al.* 1993*a*). No effect of medication was seen in the areas where the depressed patients had the most significant decreases in rCBF compared with normal controls. In the present study, for clinical and ethical reasons, we were able to re-examine 15 of the 25 patients who recovered in an optimally matched state as regards medication. The analysis of the changes in rCBF of this subgroup from the depressed to the recovered state is therefore less confounded by heterogeneity of treatment and shows that it is the changes in the left DLPFC and the medial prefrontal cortex including anterior cingulate that are the most significant.

Functional correlations

DLPFC

An important factor for any biological marker is its specificity to an individual disease, in this case, depressive disorder. We have previously discussed the implications of decreased blood flow in the DLPFC (Bench *et al.* 1993*a*). In depression and schizophrenia there is a considerable overlap in findings from functional imaging studies. For example, patients with either diagnosis have decreased perfusion in the left DLPFC. This common neurophysiological deficit is accounted for by shared phenomenology across those diagnoses. Left DLPFC hypoperfusion is strongly associated with an impairment in the internal generation of actions, irrespective of diagnosis (Dolan *et al.* 1993). This is manifest, in depression, as psychomotor retardation and, in schizophrenia, as psychomotor poverty (Liddle *et al.* 1992). Other authors have postulated that perturbed function in the left ventrolateral prefrontal cortex (VLPFC) may reflect different cognitive components of depression, such as the automatic association with emotion of concepts held in representational memory, depressive ruminations, or the inability to shift emotional or cognitive sets appropriately (Drevets *et al.* 1992).

We propose that in any one patient the distribution of rCBF or rCMRGlu will relate to symptomatic manifestations of the illness, rather than diagnosis *per se*. In this study the DLPFC shows the most significant change in activity from the depressed to the recovered state. Clearly this should have significance in terms of symptomatic change. At the index assessment we were able to show symptomatic specificity to the profile of rCBF changes in that decreased perfusion in the left DLPFC correlated significantly with a factor loading for mood and psychomotor slowing (Bench *et al.* 1993*a*). We did not perform a detailed longitudinal assessment of the change in psychomotor retardation on recovery and so are unable to determine whether the changes in rCBF in the DLPFC correlate significantly with improved 'retardation' scores. Nevertheless, we would predict that decreases in the degree of psychomotor retardation would be associated

with parallel increases in rCBF in the DLPFC. We were able to test our hypothesis that the relationship with symptoms in the DLPFC is a state phenomenon by correlating the original factor scores (Bench *et al.* 1993*a*) with the adjusted rCBF profile in the recovered scans. This analysis failed to show any significant correlations with any of the factor scores in the DLPFC even at the lowest level of significance ($P < 0{\cdot}05$). Indeed no significant correlations were seen for either of the first two clinical factors previously described. The third factor, which weights heavily for a global measure of cognitive performance, is discussed below.

Medial prefrontal and cingulate cortex

In this report we have identified how different regions within the medial prefrontal cortex, including the cingulate, change with recovery from depression. Specifically, rCBF in the superior pregenual region of the cingulate (BA 32) is decreased in the depressed state but significantly increases ($> 6\%$) to the recovered state. This area was described in our initial cross-sectional studies (Bench *et al.* 1992, 1993*a*). The paired comparison of depressed and recovered patients optimally matched for medication identifies the pregenual region of the cingulate on the right as showing the most significant increases in rCBF with recovery.

The cingulate cortex is one of the critical brain areas implicated in the expression and modulation of emotion (Papez, 1937; MacLean, 1952). Bilateral cingulate lesions involving areas 24 and 32 may cause a state of akinetic mutism (Nielsen & Jacobs, 1951; Barris & Shuman, 1953), and cingulotomy has been used beneficially for the relief of chronic depression, anxiety and pain (Foltz & White, 1962; Ballantine *et al.* 1987). The extensive neuroanatomical connections of the anterior cingulate, with both higher association and limbic regions, are consistent with its putative role in the mediation of motivational and emotional states (Mesulam, 1983). Although area 32 has been considered part of the prefrontal cortex rather than anterior cingulate, its long connections are primarily with area 24 of the anterior cingulate and with retrosplenial cortex (Pandya & Yeterian, 1985). The cingulate proper is a large, functionally heterogeneous structure. Electrical stimulation studies show that specific effects including arousal, heightened attention, simple movements or affective changes can be elicited according to the site of stimulation within the cingulate (Damasio & Van Hoesen, 1983). Consistent with these observations are findings of increased anterior cingulate activity in a range of PET activation studies involving attention, response selection, language, and pain perception (Petersen *et al.* 1988; Corbetta *et al.* 1990; Pardo *et al.* 1990; Frith *et al.* 1991; Talbot *et al.* 1991; Bench *et al.* 1993*b*). The foci of these activations extend across the length of the anterior cingulate and involve Brodmann's areas 24 and 32. In addition, memory deficits in depression correlate with decreased blood flow in medial prefrontal cortex including the pregenual region of the cingulate (BA 32) (Dolan *et al.* 1994). In view of the functional heterogeneity of the cingulate we conclude that differential changes seen within the cingulate on recovery from depression relate to the relative change in severity of various dimensions of depression.

We tested our hypothesis that the relationship with symptoms in the medial prefrontal and cingulate cortices is a state phenomenon by correlating the original factor scores (Bench *et al.* 1993*a*) with the adjusted rCBF profile in the recovered scans. Both the third factor, which loads heavily for global cognitive function (includes the MMSE), and the raw MMSE scores correlated significantly with rCBF in the recovered state in the medical prefrontal cortices including the anterior cingulate ($P < 0{\cdot}05$). Although the MMSE is a test of global function only, the correlations with this score suggest that there may be subtle persisting neurophysiological deficits seen in this area in comparison with normal controls that are related to persisting degrees of cognitive impairment. This is consistent with neuropsychological studies of depression which have shown that impairments on tests of memory and learning persist in up to 35% of patients on recovery (Abas *et al.* 1990). Dolan *et al.* have shown that, in the depressed state, there are significant correlations between scores for memory performance and attention and rCBF in the medial prefrontal cortex (Dolan *et al.* 1994). Austin *et al.* (1992*b*) have argued that impairment of memory and psychomotor speed is a core feature of depressive illness (Austin *et al.* 1992*b*). Residual cognitive deficits on recovery from de-

pression may thus be the neuropsychological correlate of subtle persisting perfusion deficits and possibly represent trait markers for recurrent illness.

Posterior parietal cortex

We have previously described decreased blood flow in the region of the angular gyrus in depressed patients in comparison with normal controls (Bench *et al.* 1992). Decreased blood flow in this region was statistically the most significant finding in a recent study of depressed patients using similar methodology (Drevets *et al.* 1992). A similar finding has also been described in a study using xenon inhalation (Sackeim *et al.* 1990). Within the posterior parietal cortex the inferior parietal lobule can be subdivided on an anatomical basis into supramarginal and angular gyri. Functional compartmentalization of the posterior parietal cortex is evident in non-human primates where several specialized regions characterized by distinctive connections with sensory and limbic systems have been described (Goldman-Rakic, 1988). Based on anatomical evidence it would appear therefore that the separate subdivisions of posterior parietal cortex, by virtue of distinctive connectivity, are specialized for different, though possibly related, information processing functions. The parietal region we have identified is made up of both polymodal (banks of superior temporal sulcus) and supramodal (inferior parietal region) association cortex. This latter area has the cingulate gyrus as its only direct limbic target (Mesulam *et al.* 1977). Thus, although the functions of the angular gyrus are multimodal, data from lesion studies in primates and human clinical studies imply a role in visuospatial orientation and attention, and in particular to stimuli that are of significance to the organism. In a detailed study of neuropsychological function in a subgroup of the present patients, significant associations were evident between attention and memory related functions and rCBF in this parietal region (Dolan *et al.* 1994). The failure to detect a significant increase in rCBF in this region in the matched sample may be a correlate of continuing symptomatology, possibly affecting attention and memory (despite satisfying criteria for 'recovery'), and/or represents a neurophysiological trait marker for susceptibility to depression.

Recovery to normal?

In the present study the normal controls were only scanned on one occasion and so are not a good control group for the recovered scans. For this reason we have not formally reported the results of the comparison between recovered scans and normal controls. However, our explorative analysis suggests that the medial and lateral cortical deficits are only detectable at levels of significant ($P < 0{\cdot}05$) at which false positives occur at an unacceptable rate (Bailey *et al.* 1991). Decreased perfusion in the angular gyrus is detectable at the $P < 0{\cdot}01$ level and we tentatively suggest that this finding raises the possibility of non-reversible deficit. Longitudinal scanning over a more extensive time period than was feasible in the present study and re-examination of the normal control could determine whether the blood flow in these areas normalizes over time.

Correlations with depression severity

We failed to establish significant correlations between rCBF and global measures of depression severity (HAM-D and MADRS) in the depressed state. This is not surprising since global scores, by definition, do not discriminate between particular symptoms or clusters of symptoms. Since focal deficits in rCBF in depression relate to particular symptomatic profiles we would not expect significant correlations with a global score in those areas. Where significant correlations with global scores have been found, they are often difficult to interpret. Austin *et al.* (1992*a*) found significant negative correlations with HAM-D scores and prefrontal rCBF after controlling for scores on the Newcastle endogenicity scale (Carney *et al.* 1965). Drevets *et al.* (1992) have reported a positive correlation with HAM-D scores and rCBF in the amygdala (although rCBF here did not decrease on recovery) but a negative correlation in the left prefrontal cortex. They reported that increased rCBF in the ventrolateral prefrontal cortex was associated with negative ruminations, and that with increasing severity of depression, as indexed by an increase in the HAM-D score, negative thoughts diminished in frequency as thoughts 'slowed down'. This suggests that the most severely depressed patients should have relatively lower rCBF. In

comparison with the present study, the severity of depression was comparable. The most likely reason for the discrepancy in the results would seem to be the differences in criteria for patient selection.

The present study shows that there are demonstrable changes in cerebral neurophysiology on recovery from depression. The mediating mechanisms of these changes are unclear and might relate to events such as changes in synaptic strength or alterations in the function of neuromodulatory inputs. In terms of the latter possibility it is striking that the most significant changes with recovery occur in the left DLPFC and the medial prefrontal cortex including anterior cingulate. Among the neurotransmitter systems that may have a role in the pathogenesis of affective disorders, dopaminergic inputs exhibit the greatest degree of topographic specificity, and have particularly high concentrations in the anterior cingulate and prefrontal cortices compared to other cortical sites (Brown *et al.* 1979; Berger *et al.* 1991). Some of the cognitive and behavioural deficits of patients with Parkinson's Disease that have been thought to reflect decreased dopaminergic function are phenomenologically similar to the symptoms of retarded depression (Scatton *et al.* 1982).

However, the dopaminergic theory in depression is complex. The electrophysiological evidence is that dopamine has a profoundly inhibitory effect on cortical neurons, but dopaminergic agonists may increase rather than decrease prefrontal metabolism in animals (McCulloch *et al.* 1982). Behavioural studies suggest that mesocortical dopaminergic projections facilitate the function of the prefrontal cortex with lesions of ascending projections causing impaired prefrontal performance in primates (Brozowski *et al.* 1979; Saper, 1987). These effects may be explained by the putative role of dopamine as a neuromodulator rather than a neurotransmitter in the cortex (Bunney & Chioda, 1984). Manipulation of dopaminergic neurotransmission in novel functional imaging paradigms adds more evidence for the role of dopamine in prefrontal cerebral function. Grasby *et al.* (1993) demonstrated an increase in rCBF in the anterior cingulate and dorsolateral prefrontal cortices bilaterally in normal volunteers after the administration of apomorphine, a non-selective dopaminergic agonist. Many antidepressant treatments enhance dopaminergic activity and the topography of some of the changes described in the present study might be consistent with increases in dopaminergic neurotransmission on recovery from depression.

The basal ganglia are extensively innervated with dopaminergic neurons from the substantia nigra and ventral tegmental area. Some studies have described decreased resting state rCBF or metabolism in the basal ganglia (caudates) in depression (Baxter *et al.* 1985; Buchsbaum *et al.* 1984, Cohen *et al.* 1989; Austin *et al.* 1992*a*; Drevets *et al.* 1992) and there is limited evidence that antidepressant medication may increase basal ganglia metabolic rate in these patients to normal (Cohen *et al.* 1989; Drevets & Raichle, 1992). However, the present study, among others (Kling *et al.* 1986; Kanaya & Yonekawa, 1990; Hurwitz *et al.* 1990; Martinot *et al.* 1990; Cohen *et al.* 1992), does not find these changes. There are several possible explanations for this negative result. First, it may reflect differences between studies in patient selection and medication status. Secondly, perhaps the SPM analysis is insensitive to changes in the basal ganglia. Although the stereotaxic normalization of images is weighted towards cortical data it has been shown that the precision of image registration is as accurate for subcortical structures (thalamus and putamen) as it is for cortical structures (Friston *et al.* 1991*b*). In addition, several PET studies using appropriate activation paradigms and SPM analysis have demonstrated basal ganglia activation (Playford *et al.* 1992; Jenkins *et al.* 1993). Thirdly, Krishnan *et al.* (1992) have described reduced caudate volume in depression and this could appear as decreased CBF or glucose metabolism in low-resolution PET or SPECT images, particularly with region of interest analysis.

It is possible that a dopaminergic deficit in depression may be confined to the mesolimbic/mesocortical projections originating in the ventral tegmental area (VTA) rather than the substantia nigra. Physiological differences in the regulation of the mesostriatal and mesocortical dopaminergic systems have been discussed elsewhere (De Keyser *et al.* 1990). In such an instance we would expect dopaminergic induced changes in synaptic activity, and consequently rCBF or metabolism, in several cortical areas

including the lateral and medical prefrontal cortex.

In summary, the present study indicates that there are significant increases in rCBF on clinical recovery in areas previously identified as having decreased rCBF in the depressed state. We are unable to say whether the values return to normal. There appears to be a persisting positive correlation between medial prefrontal/cingulate rCBF and neuropsychological function on recovery. The significance of the latter result can only be a matter of speculation, but one possibility is that rCBF in this region eventually does normalize, with the period up to normalization representing a risk period for relapse. The most recent clinical studies suggest that the time scale of follow-up necessary to evaluate this possibility is likely to be at least five years (Kupfer *et al.* 1992). An alternative possibility is that medial prefrontal rCBF deficits and associated deficits in memory and attention are true trait markers for depression and are manifestations of a biological vulnerability for the disorder.

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