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The anatomy of melancholia – focal abnormalities of cerebral blood flow in major depression

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SYNOPSIS Using positron emission tomography (PET) and ^{15}Oxygen, regional cerebral blood flow (rCBF) was measured in 33 patients with primary depression, 10 of whom had an associated severe cognitive impairment, and 23 age-matched controls. PET scans from these groups were analysed on a pixel-by-pixel basis and significant differences between the groups were identified on Statistical Parametric Maps (SPMs). In the depressed group as a whole rCBF was decreased in the left anterior cingulate and the left dorsolateral prefrontal cortex ($P < 0{\cdot}05$ Bonferroni-corrected for multiple comparisons). Comparing patients with and without depression-related cognitive impairment, in the impaired group there were significant decreases in rCBF in the left medial frontal gyrus and increased rCBF in the cerebellar vermis ($P < 0{\cdot}05$ Bonferroni-corrected). Therefore an anatomical dissociation has been described between the rCBF profiles associated with depressed mood and depression-related cognitive impairment. The pre-frontal and limbic areas identified in this study constitute a distributed anatomical network that may be functionally abnormal in major depressive disorder.

INTRODUCTION

Major depression is a common illness, with an annual incidence of 0·4–2·7 per 1000 (Nielsen, 1976; Helgason, 1977) and a lifetime prevalence of up to 6·7% (Robins *et al.* 1984). Increasing age and genetic loading are among the most potent risk factors for severe depression. Although presenting most commonly as mood disturbance, depression may also present under a number of other guises including psychomotor disturbance and cognitive impairment, so-called depressive pseudodementia. This latter presentation may lead to a misdiagnosis of primary degenerative dementia (Marsden & Harrison, 1972).

The mediating biological mechanisms in depression are unknown. A guiding assumption in research is that depression is associated with functional disturbance in one or more cerebral monoamine pathways. Evidence implicating specific monoamine systems is indirect and based largely on examination of bodily fluids, such as CSF (van Praag *et al.* 1970), or inferred from abnormal neuroendocrine responses to specific probes (van Praag, 1982). Cell bodies of the monoamine systems are localized to the brainstem and send relatively diffuse projections to subcortical and cortical structures. Whether the proposed abnormalities are anatomically localized or globally distributed is not specified by the monoamine theories, although the limbic system is frequently invoked as a likely site of perturbed function. Consequently the precise neuroanatomical systems involved in depression and its associated impairments such as the cognitive impairment of depression have not been defined.

Developments in functional imaging techniques offer new possibilities for exploring brain behavioural relationships in the major psychiatric syndromes. In the adult brain neuronal activity is closely linked to regional blood flow (rCBF) and metabolism of oxygen and glucose. Positron Emission Tomography (PET)-

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derived measures of rCBF and metabolism are a sensitive and reliable index of local neuronal function (Raichle, 1987), and such measures may be used to explore the functional anatomy of specific psychiatric disorders. Using PET, regional decreases in glucose metabolic rates have been reported in bipolar and unipolar depressed patients with normalization on clinical recovery (Baxter *et al.* 1985). We report a PET study of regional cerebral blood flow in depressed subjects, combined with statistical parametric mapping (Friston & Frackowiak, 1991), which identifies dissociations between focal abnormalities in cerebral function due to mood disturbance on the one hand and associated cognitive impairment on the other.

METHOD

Patients and Controls

Patients with an upper age limit of 75 years were recruited from a regional psychiatric service and from a national referral centre. Potential participants were approached to ascertain willingness to co-operate with the study and ability to give informed consent. In those who consented, the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer, 1978) was administered. Patients who met Research Diagnostic Criteria (RDC) (Spitzer *et al.* 1977) for major depressive disorder were further evaluated, and excluded if there was a history of organic brain disease, drug or alcohol abuse or significant medical illness as assessed by clinical examination and haematological, biochemical and endocrinological parameters. Subjects were also excluded if they scored over 4 on the Hachinski ischaemic scale (Hachinski *et al.* 1975) or had evidence of focal abnormality on CT or MRI scans. Patients on psychotropic medication (19 of the 33) were entered into the study, as it was predicted that patterns of rCBF would reflect their depressed mental state rather than medication – a prediction which could be tested. The inclusion of medicated patients also allowed the examination of patients in whom drug washout was not ethical. Of the medicated patients nine were taking tricyclic antidepressants alone and one was taking a monoamine oxidase inhibitor. In the remaining nine patients medication additional to tricyclics included neuroleptics ($N = 5$), lithium ($N = 2$), carbamazepine ($N = 1$) and tryptophan ($N = 2$). Of the unmedicated patients, six were drug naive, two had been drug-free for greater than 1 year and five had been drug-free for over 2 weeks. A single patient who had been taking antidepressants erratically was drug-free for 2 days. All patients had moderate to severe depression as rated on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960) and on the Montgomery and Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979). Handedness was assessed according to Oldfield (Oldfield, 1971). Those subjects who satisfied the entry criteria received a comprehensive battery of neuropsychological tests, designed specifically to target cognitive functions thought to be impaired in depression. These data will be presented elsewhere. PET scans were performed with 3 days of neuropsychological assessment. This 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 ^{15}Oxygen was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC). All subjects gave informed written consent. Demographic data are presented in Table 1. PET studies of 18 control subjects were taken from the library of normal scans available at the MRC Cyclotron Unit and supplemented with five subjects recruited prospectively by local advertisement. None of the controls had a history of psychiatric or significant medical illness, nor were they taking psychotropic medication (Table 1).

Table 1. *Characteristics of the patients and controls*

	Depressed	Controls
Number	33	23
Sex (M/F)	21/12	10/13
Age (yr mean ±S.D.)	56·8 (±12·8)	63·4 (±11·6)
Handedness (R/L)	30/3	22/1
Psychotropic medication (±)	19/14	—
HAM-D 17-item (mean ±S.D.)	25 (±4·1)	—
MADRS (mean ±S.D.)	30 (±5·5)	—
Unipolar/Bipolar	30/3	—

PET scanning

All patients and controls underwent steady-state measurement of cerebral blood flow using PET

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Image and statistical analysi

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an ±S.D.)	30 (±5·5)	—
›.)	30/3	—

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nd $C^{15}O_2$ inhalation. Studies were performed in e supine position in a room with dimmed ghts and minimal noise other than that of the anner's cooling system. For each subject a olystyrene head mould was made which was ed to ensure correct positioning in the scanner id relative head immobility. A 22 g Teflon annula was inserted into a radial artery after llen's test for collateral circulation and infiltra- on of the skin with 1% Marcain (Bupivicaine). ubjects were aligned in the scanner with eference to a laser-beam system so that the tectors were parallel to the orbito-meatal OM) line. They were asked to close their eyes uring the study, but no other instructions were iven. Measured attenuation corrections of the mission scans were made with the ratio of ounts in blank and transmission scans obtained sing a ^{68}Ge ring source. After attenuation orrection the raw emission data were trans- ormed into parametric images of CBF using the hole-blood and plasma activities measured uring the scans. Details of these methods have een previously described (Frackowiak *et al.* 980). After reconstruction and filtering the ixel size was 2·05 mm^2 and the image resolution as 8·5 × 8·5 × 7·0 mm. Studies were performed sing a PET scanner (CTI Knoxville model 931-08/12 CTI PET Systems, Knoxville, ennessee, USA) whose physical performance as been described (Spinks *et al.* 1988). The etrospective control subjects ($N = 18$) were canned prior to recruitment of the patients but he prospective controls ($N = 5$) were scanned in random order with the patients. All scans were cquired using the same equipment and methods ver a two-year period.

Image and statistical analysis

mage analysis was performed on a SUN 3/60 or SPARC Workstation (Sun Microsystems Europe Inc., Surrey, UK). The 15 original planes of data within the 10·5 cm field of view of the scanner were interpolated to 43 planes to render the voxels approximately cubic. The images were checked for artefacts and corrected for yaw and roll. To enable inter-subject averaging of scan data the images were then resized into a standard stereotactic space. The reference plane for this transformation was the intercommissural (AC-PC) line, which was identified directly from anatomical landmarks in the PET image (Friston *et al.* 1989). The 43 planes of data were then resliced into the standard stereotactic space (Talairach & Tournoux, 1988). In this space each pixel represents 2 × 2 mm and the 26 new planes are 4 mm thick. The images were smoothed with a Gaussian filter to reduce the effect of individual variability in cortical gyral anatomy. Smoothing allows the constructive interference of equivalent sites of difference when images are averaged. This initial transformation of the data allowed subsequent analysis to be entirely data led and not subject to bias imposed by observer placement of regions of interest on the images.

Following stereotactic normalization the CBF images were adjusted for individual differences in global blood flow using an analysis of covariance (ANCOVA), as previously described (Friston *et al.* 1990). This procedure generated an adjusted mean blood flow map for each of the pooled groups (e.g. depressed and controls) and permitted an estimate of the error variance of the rCBF in each pixel. Group-by-group comparisons were then made on a pixel-by-pixel basis using the t statistic to compare adjusted (for whole-brain CBF) group means. The resulting statistical parametric maps (SPMs) of t values were displayed within the standard stereotactic space, plane by plane and as projections on to sagittal, coronal and transverse renderings of the brain.

In order to identify foci of significant difference throughout the brain volume without false positives, a threshold for significance was used to take into account the multiple simultaneous t tests performed. The (t)SPMs were therefore thresholded with a Bonferroni correction for repeated measurements (Friston *et al.* 1991). Although in practice the t tests were carried out on every pixel, the number of truly independent sites was far fewer, because neighbouring pixels are correlated due to averaging and smoothing. The correction applied corresponds to an expected false-positive rate of 1 per 20 planes.

RESULTS

Comparing the 33 depressed patients and 23 controls the (t)SPM identified two areas in the depressed group which showed significantly reduced rCBF. These areas were the left anterior

Table 2a. *Co-ordinates of the pixels where the most significant differences in blood flow were identified. Co-ordinates refer to the stereotaxic atlas of Talairach and Tournoux. The CBF values are in units of ml/dl tissue/min, and have been adjusted for a global mean blood flow of 50 ml/dl/min. 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*

Location	Co-ordinates			Regional CBF		Z score
	x	y	z	Controls	Depressed	
(L) Anterior cingulate cortex	−14	24	36	57·4	54·5	3·46**
	−16	18	40	57·1	54·3	3·48**
(L) Dorsolateral prefrontal cortex	−38	34	20	50·0	47·4	3·74**

** $P < 0{\cdot}05$ Bonferroni-corrected.

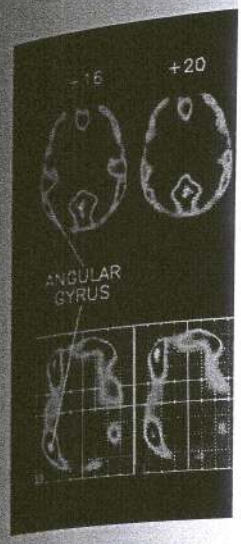
Table 2b. *Blood flow in medicated and unmedicated patients at the regions where maximum difference was found in depressed patients compared with normal controls. The groups have been compared using an unpaired t test. The CBF values are in units of ml/dl tissue/min, and have been adjusted for a global mean blood flow of 50 ml/dl/min. Statistical maps at a threshold of P < 0·01 (non-corrected) did not detect any significant change at these co-ordinates when medicated and unmedicated patients were compared*

Location	Co-ordinates			Regional CBF			
	x	y	z	Unmedicated	Medicated	*t*	*P*
(L) Anterior cingulate cortex	−14	24	36	54·9	54·3	0·64	0·53
	−16	18	40	54·9	53·7	1·15	0·26
(L) Dorsolateral prefrontal cortex	−38	34	20	47·9	47·1	0·93	0·36

cingulate and the left dorsolateral prefrontal cortex respectively (Fig. 1). The CBF values for the pixels of maximum significance normalized to a global mean of 50 ml/dl/min are presented in Table 2. The first area identified was in the superior/anterior cingulate cortex (Brodman's Area 32). This was centred at +36 mm with respect to the AC–PC line and extended from +32 mm to +40 mm. Results for the left dorsolateral prefrontal cortex (DLPFC) (BA 9,46) were of a similar order of significance and spread from +16 mm to +28 mm with respect to the AC–PC line. The most significant pixel was at +20 mm. The right DLPFC showed a strong trend to decreased blood flow (+24 to +28 mm), but did not survive Bonferroni correction. Two other regions in the depressed-patient sample also showed strong trends toward significant differences in rCBF ($P < 0{\cdot}001$ non-Bonferroni-corrected). An increase in CBF was localized to the left posterior cingulate gyrus (BA 23,30). A decrease in CBF was localized to the left angular gyrus (BA 39) confluent with the superior aspect of the superior temporal sulcus (Fig. 1).

To test the prediction that the effects of medication were not confounding the changes due to psychopathology, a second comparison was made between medicated ($N = 19$) and unmedicated ($N = 14$) depressives. This comparison was made at a lower threshold ($P < 0{\cdot}01$), non-Bonferroni-corrected). No significant changes in rCBF were found at the regions previously identified. This finding does not allow the rejection of the null hypothesis that medication has no effect, but does indicate that medication effects cannot account for the profile of differences in rCBF between the depressed patients and controls. The rCBF values for medicated and unmedicated patients are presented in Table 2b.

A third comparison was made to examine specific changes within the depressed group associated with cognitive impairment. The patients were subdivided into three groups on the basis of their scores on the Mini-Mental



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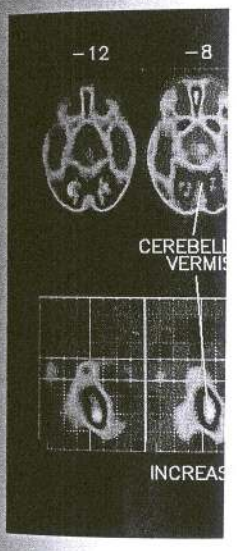

FIG. 2. (*t*)SPM showi
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White areas are *t* value

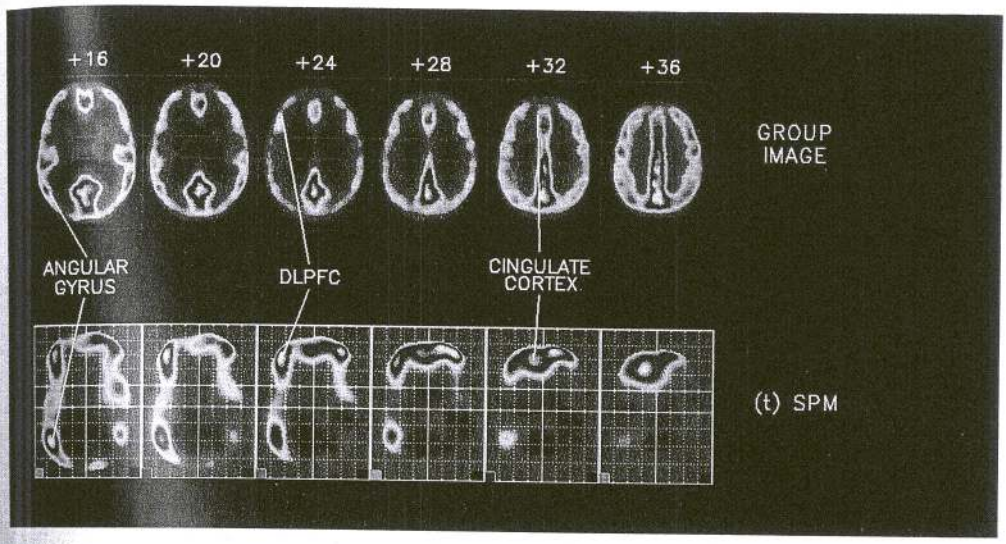

FIG. 1. Statistical parametric maps (*t*)SPM showing location of significant decreases in rCBF in the depressed group as a whole in comparison with the normal controls. White areas are *t* values at $P<0{\cdot}001$. The most significant decreases, in the left dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex, survive Bonferroni correction ($P<0{\cdot}05$). The group image is included for reference to show anatomical detail and is the average of the stereotactically normalized CBF data set from the 23 normal subjects. The choice of colour scale of the group image is arbitrary; in this case a rainbow scale is used with blue corresponding to lowest blood flow and white to highest. Numbers (e.g. +16) refer to level of the transverse slices in millimetres relative to the AC–PC line. Anterior is at the top of the image and the subjects' right is at the right. The grid corresponds to that used by Talairach & Tournoux (1988).

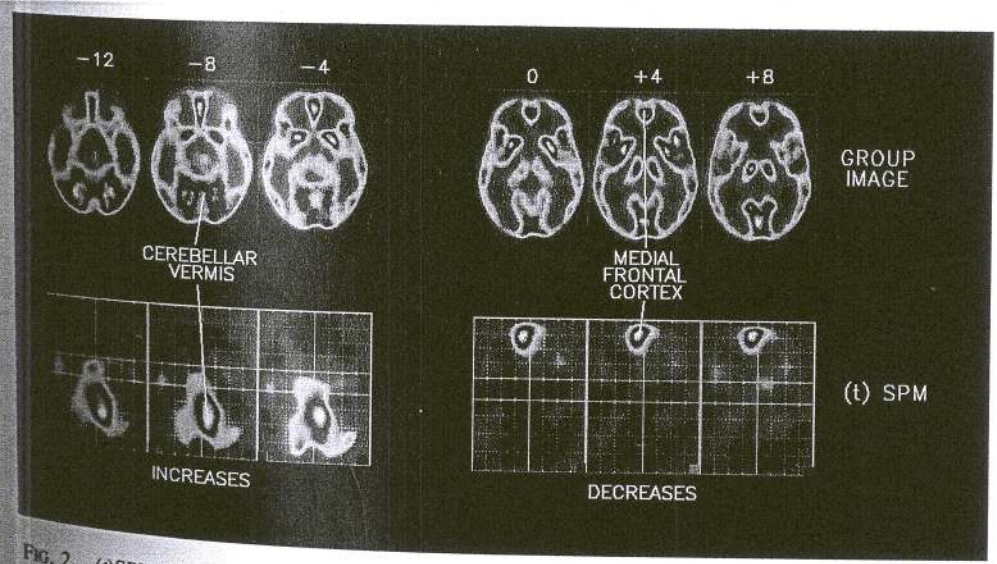

FIG. 2. (*t*)SPM showing location of significant increases (left) and decreases (right) in rCBF when the cognitively impaired depressed group is compared with non-cognitively impaired depressed patients. White areas are *t* values at $P<0{\cdot}05$ Bonferroni corrected.

(*Facing p.* 610)

Table 3. *Characteristics of depressed patients with and without cognitive impairment as defined by their scores on the Mini-Mental State Examination*

	Cognitively impaired depressed (MMSE ⩽ 25)	Cognitively unimpaired depressed (MMSE ⩾ 29)
Number	10	10
Age (yr mean ±S.D.)	60·9 (±7·8)	53·2 (±14·8)
HAM-D 17-item (mean ±S.D.)	25·7 (±4·2)	24·4 (±3·5)
Psychotropic medication (±)	8/2	4/6

State examination (MMSE). On this measure ten patients were unimpaired (score ⩾ 29) and ten were impaired (score ⩽ 25), while the remaining 13 patients achieved intermediate scores and were excluded from the subsequent analysis. These impaired patients also scored 85 or less on the CAMCOG subscale of the CAMDEX, which incorporates all of the items of the MMSE. The correlation between CAMCOG and MMSE scores within the depressed group was 0·93 ($P < 0·001$). The impaired and unimpaired groups were matched for age and severity of depression (Table 3). Comparing scans from the impaired and unimpaired groups the (*t*)SPM, Bonferroni-corrected, identified foci of significant change in the depressed cognitively impaired group. These consisted of decreases in rCBF in the left medial prefrontal cortex (BA 10) (0 mm to +12 mm) and increases in rCBF in the right aspect of the cerebellar vermis (−12 mm to −4 mm) (Fig. 2). The co-ordinates of the most significant pixels and magnitude of changes are shown in Table 4.

A fourth and final comparison was made between the cognitively impaired depressed group ($N = 10$) and the controls ($N = 23$). As predicted, this analysis showed significant changes in rCBF characteristic of both the cognitive impairment of depression and major depression, i.e. decreases in the left medial frontal and dorsolateral prefrontal cortices and the anterior cingulate, and increases in the cerebellar vermis.

DISCUSSION

These findings indicate that functional changes in the left anterior cingulate and the DLPFC are associated with the syndrome of major depression, while additional changes in the medial prefrontal cortex are associated with the cognitive impairment of depression, so-called depressive pseudodementia. The findings offer direct *in vivo* evidence of limbic system involvement, specifically the anterior cingulate cortex, in the pathogenesis of depression. Using the Xenon-133 inhalation technique, reductions in rCBF have been described in selective frontal, central, superior temporal and anterior parietal regions (Sackeim *et al.* 1990). Previous PET studies of depressed patients have found decreased metabolism in the inferior frontal lobe (Buchsbaum *et al.* 1984). More specific findings include lower hemispheric metabolic rates in bipolar patients (Baxter *et al.* 1985), relative caudate hypometabolism in unipolar patients

Table 4. *Co-ordinates of the pixels where the most significant differences in blood flow were identified. Co-ordinates refer to the stereotaxic atlas of Talairach and Tournoux. The CBF values are in units of ml/dl tissue/min, and have been adjusted for a global mean blood flow of 50 ml/dl/min. 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*

Location	Co-ordinates			Regional CBF		
	x	y	z	Impaired	Unimpaired	*Z* score
(L) Medial frontal cortex	−8	48	0	57·2	62·6	3·98**
	−6	52	4	55·1	60·2	4·55**
	−6	54	8	51·4	56·2	4·29**
	−6	54	12	50·1	54·1	3·56**
Cerebellar vermis	8	−66	−12	81·6	72·7	3·75**
	10	−60	−8	78·3	70·0	3·82**
	8	−48	−4	68·1	61·7	3·73**

** $P < 0·05$ Bonferroni-corrected.

(Schwartz *et al.* 1987) and impaired left DLPFC metabolism in both subgroups (Baxter *et al.* 1989).

The regions implicated by this study have, as individual deficits, little specificity for depression. In particular, functional abnormalities in the left DLPFC appear to be common to a number of major psychiatric syndromes (Weinberger *et al.* 1986). However, the pattern of deficits described in the present study may constitute a profile unique to the depressive syndrome. Although each regional deficit is associated with a symptomatic or neuropsychological component that is a part of the syndrome of depression, it can also be seen in other disorders. For example, impaired higher-order cognitive function and a left medial prefrontal deficit appear to be common to depressive pseudodementia and psychomotor poverty syndrome of schizophrenia (Liddle *et al.* 1990). Thus, functional deficits in this area may provide the basis for higher cognitive impairments seen in the major psychoses. The pattern of decreased rCBF in the medial prefrontal area is also distinct from the characteristic metabolic changes seen with cognitive impairment and a different neuropsychological profile in the more common neurodegenerative and vascular dementias (Frackowiak *et al.* 1981).

The lateralization of the significant decreases in rCBF to the left hemisphere is striking. Previous work on lateralization has tended to implicate the right hemisphere in the pathogenesis of depression (Flor-Henry, 1979). The findings in this study are consistent with some investigations of stroke patients which show that left-hemisphere lesions are associated with depression, and severity of depression correlates with the proximity of the lesion to the anterior pole of the left hemisphere (Robinson *et al.* 1983, 1984). This is a contentious area of research, and other studies have shown that the relationship with site of lesion is not upheld when the patient sample includes non-in-patients interviewed using standardized instruments (House *et al.* 1990; Sharpe *et al.* 1990).

Significant and non-significant changes in rCBF were noted in the cerebellum and posterior cingulate respectively. The pattern of significantly increased blood flow in the cerebellar vermis was unexpected. However, a number of converging lines of evidence implicate the cerebellum in the regulation of emotion. The midline cerebellum (vermis and fastigial nucleus) has previously been demonstrated to be an integral part of a neural network for emotional expression with anatomical connections and functional relationships to the limbic system (Heath & Harper, 1974; Heath *et al.* 1978). Several case reports have described affective concomitants of vermal pathology (Heath *et al.* 1979; Hamilton *et al.* 1983). In a PET study of patients with anxiety disorder increased blood flow in the cerebellum was observed (Reiman *et al.* 1989).

Structural imaging was not performed routinely in the depressed patients, but 15 of the 33 had CT or MRI scans. No focal abnormalities were reported in these scans, although atrophic or involutional changes were reported in 3 of the 15. It is known that a proportion of depressed patients display CT evidence of structural brain change (Dolan *et al.* 1985, 1986). These abnormalities are generalized, unrelated to clinical features of depression and more pronounced in elderly subjects. Although the majority of studies have found these changes to be non-progressive, a recent report has raised the possibility of progressive loss of tissue in the temporal lobes with increasing duration of illness (Altshuler *et al.* 1991). Depressed patients with cognitive deficits may have ventricular brain ratios (VBRs) intermediate in size between those of depressed cognitively normal patients and patients with probable Alzheimer's disease (Pearlson *et al.* 1989). It seems unlikely that neuronal loss secondary to gross structural changes can account for the regional functional abnormalities we have described. Previous studies of Alzheimer's disease have shown that the majority of metabolic abnormalities identified by PET cannot be explained by cortical atrophy (Fazekas *et al.* 1989). It would require a systematic difference in brain structure, for example cortical thinning, within the depressed group to lead to the profile of abnormalities described in this study. Even if a component of the functional changes described is due to structural differences, either macroscopic or microscopic (decreases in synaptic or neuronal density), the regional specificity remains of great interest.

Psychotropic medication failed to account for the differences found, suggesting that the main

source of change in rCBF was due to the depressed mental state. The depressed patients were mainly at the same (early) phase of their illness and treatment. It is conceivable that rCBF normalizes over a time scale which parallels the therapeutic effects of antidepressants. Studies have shown that reductions in glucose metabolism in the left DLPFC normalize with antidepressant medication and improvement of depression (Baxter *et al.* 1989; Martinot *et al.* 1990). Follow-up scans in the recovered phase will identify whether the changes observed, in particular those specific to the cognitively impaired group, are reversible, static or progressive.

The limbic system, particularly the cingulate gyrus, has long been implicated in either the expression (Papez, 1937) or modulation (MacLean, 1952) of emotion. Papez, in his classic formulation of the role of the limbic system, speculated that 'radiations of emotive processes from the gyri cinguli to other regions in the cerebral cortex would add emotional colouring to psychic processes'. The surgical procedure of cingulotomy has been used with reported success in both resistant depression and intractable pain. The efficacy of such procedures suggests that the cingulate imparts emotional tone to lower-order perceptions. Cingulotomy for intractable pain does not abolish the sensation of pain, but rather extinguishes the associated unpleasant effect (Foltz & White, 1962). Among cerebral structures the cingulate gyrus shows the greatest functional decrease in rCBF with age (Martin *et al.* 1991). This selective vulnerability of anterior cingulate activity may provide a biological basis for the increased incidence of major depression in older age groups.

The role of the cingulate as an attentional centre has recently been investigated using PET (Pardo *et al.* 1990). The cingulate area highlighted was inferior and posterior to the area identified in the present study. It is noteworthy that attentional impairments are an invariable symptom in depressive illness. The proximity of these two centres demonstrated in separate studies could implicate a more widespread involvement of the anterior cingulate in depression. These data lend support to the view that the cingulate can be considered an interface between attention and emotion (Powell & Hines, 1974). A non-significant increase in rCBF was noted in the left posterior cingulate (BA 23). The anterior and posterior cingulate have reciprocal anatomical connections, and the increase in rCBF supports a notion of functional as well as anatomical coupling (Baleydier & Mauguière, 1980).

The importance of the pre-frontal focal abnormalities described in the present study is highlighted by primate studies which indicate a pattern of reciprocal connections between the anterior cingulate, the dorsolateral pre-frontal cortices and the medical frontal cortices (Pandya *et al.* 1981). The pre-frontal areas are therefore sites of convergence for limbic inputs with highly processed associative information, and may serve the function of integration of thought and emotion (Mesulam, 1986). Such structures would, therefore, seem to be part of an extended neural network, whose functions include the regulation of mood and directed attention, which is disturbed in major depression.

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