British Journal of Psychiatry (1990), **157** (suppl. 9), 76–81

A Study of Depression in Old Age Using Single-Photon Emission Computerised Tomography

A. K. UPADHYAYA, M. T. ABOU-SALEH, K. WILSON, S. J. GRIME and M. CRITCHLEY

There is evidence to suggest that organic cerebral changes occur in elderly depressed patients. Quantitative studies of elderly depressed patients have demonstrated that they have reduced 'radioattenuation' on computerised tomography (CT) scans and as a group resembled more closely a group of demented patients than normal controls (Jacoby *et al*, 1983). Many biochemical changes associated with ageing are similar to the pathophysiological abnormalities in depression and in dementia (Alexopoulos *et al*, 1988). These changes, coupled with the high frequency of depressive syndromes in demented patients, suggest a complex relationship between depression and dementia in old age. Mahendra (1985) has suggested that a variety of brain abnormalities can produce a spectrum of clinical manifestations, ranging from depression with minimal cognitive dysfunction at one end to dementia with minimal depression at the other.

The advent of non-invasive neuroimaging techniques such as positron-emission tomography (PET) and magnetic resonance imaging (MRI) has facilitated the study of cerebral changes in psychiatric disorders. Recently the development of the more widely available technique of single-photon emission computerised tomography (SPECT) has led to several studies of cerebral perfusion. SPECT can be provided more cheaply than PET, and provides similar information on regional cerebral blood flow (rCBF) (Johnson *et al*, 1987). A recent study using the lipophilic compound technetium-99m hexamethylpropylenamine oxime ($^{99}Tc^{m}$-HMPAO) has validated the use of SPECT in demonstrating distinctive patterns of impaired cerebral perfusion, corresponding with discrete neuropsychological deficits in patients with Alzheimer's disease (AD) (Burns *et al*, 1989). Hypoperfusion in the parietal region has been shown to be the most consistent finding in AD and this also showed the highest correlation with the severity of dementia (Johnson *et al*, 1988).

In contrast, studies on cerebral perfusion in depressive illness have been rather limited. Matthews *et al* (1980), using xenon-133, studied 13 patients with major depressive disorder (MDD) and reported significantly reduced flow in the left hemisphere compared with that in age-matched healthy controls. Gustafson *et al* (1981) found no difference in the cerebral blood flow in depressed patients compared with that in normal controls. Uytdenhoef *et al* (1983) reported increased flow in the left frontal lobe and decreased flow in the right posterior areas in patients with MDD. Gur *et al* (1984) measured rCBF at rest and during the performance of a verbal and spatial task in depressed patients and healthy controls. In depressed male patients there was a lower than normal flow at rest, but the flow increased to normal levels during cognitive activation.

Studies of affective disorders using SPECT (Rush *et al*, 1982) have also shown lower mean rCBF in unipolar endogenous depressions, which reversed with clinical recovery. There were also significant differences in right–left asymmetry between depressed patients and normal subjects. Devous *et al* (1984) compared the rCBF in depressed patients with that of the controls and confirmed the lower flow in the right temporal and parietal lobes in patients with unipolar endogenous depression. Sackeim *et al* (1990), using a ^{133}Xe inhalation technique, showed that regional cerebral perfusion in selective frontal, central, superior temporal and anterior parietal regions was reduced compared with that in healthy controls.

Most of the SPECT studies in depressed patients have included younger people. The exception to this was the study by Sackeim *et al* (1990), which reported on subjects with a median age of 62 years. In view of the established usefulness of SPECT in demonstrating cerebral changes in dementia, and the overlap between dementia and depression in the elderly group, we used SPECT to study three groups of subjects – elderly patients with AD, age-matched controls, and patients with MDD – to examine the changes in cerebral perfusion in elderly depressed patients and to study the relationship between rCBF and severity of symptoms.

Method

Eighteen patients fulfilling the DSM-III-R (American Psychiatric Association, 1987) criteria for major depressive disorder (MDD), 14 patients satisfying the criteria of

https://doi.org/10.1192/S0007125000291873 Published online by Cambridge University Press

NINCDS-ADRDA (McKhann *et al*, 1984) for Alzheimer's disease (AD), and 12 healthy controls were studied. All subjects were right handed. The control subjects were free from serious physical illness and current or past history of mental illness. A cranial CT scan was performed in six patients with MDD and six patients with AD; some of these showed generalised cortical atrophy. The patients underwent routine laboratory screening, including full blood count, liver function tests, thyroid function tests, vitamin B12 and folate tests; the results were normal.

The subjects were assessed with the Geriatric Mental State (GMS) examination (Copeland *et al*, 1986), Mini Mental State (MMS) examination (Folstein *et al*, 1975), and Hachinski scale (Hachinski *et al*, 1975). All except seven patients with MDD were administered the Cambridge Cognitive Schedule (CAMCOG), which provides a detailed assessment of cognitive function (Roth *et al*, 1988). The findings on GMS examination were analysed with the GMS-AGECAT (Dewey & Copeland, 1986) computer program to yield psychiatric diagnosis for each subject. The depressed patients were administered the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967) and the Newcastle scale for 'endogenicity' (Carney *et al*, 1965).

The subjects underwent SPECT between 1 p.m. and 3 p.m. They were administered 550 MBq of $^{99}Tc^{m}$-HMPAO and were positioned beneath a large-field-of-view gamma camera (Siemens ZLC Orbiter: 75 tube). The camera rotated with the minimum possible radius around the subject's head. The camera motion, data processing and data acquisition were controlled by a Picker PCS 512 computer and Nuclear Diagnostics Tomographic software. Images were acquired for 30 seconds each at 64 angles and the total study time was approximately 45 minutes. A low-energy all-purpose (LEAP) collimator was used and images structured in a 64×64 matrix. A previously acquired 50-million-count flood study was used to correct the acquired data for camera non-uniformity.

Before full reconstruction, a single transaxial mid-brain slice was produced from which the elliptical dimensions of the head were determined. This provided the co-ordinate base for the attenuation correction of the reconstructed data. Image reconstruction was achieved by a filtered back-projection process and multiple transverse image slices were produced. The slice resolution was 64×64 pixels by 2 pixels thick, which corresponded to a voxel (volume element) of $0.625 \times 0.625 \times 1.25$ cm^3.

After reconstruction, the images in the transverse-section file were normalised and displayed sequentially on a colour monitor. Four relevant images from this file were selected and stored in a single 512×512 pixel image on hard disk for subsequent analysis. These images were visually inspected and reported upon by two authors (MC and SJG), who were blind to the clinical details of the subjects. Regions of interest (ROIs) identifying the frontal, temporal, parietal and occipital areas on the left and right sides of the brain were defined on these images and the average value of the counts in these ROIs were calculated. A ratio of the counts in these areas to the mean counts in a ROI defined over the right and left cerebellar region was used as an index of regional blood flow.

Statistical analysis

The ratios of radioactivity in the different regions of the brain were compared across the three groups by analysis of covariance (ANCOVA) using diagnostic group and gender as factors, and age as a covariate. Pearson's product-moment correlations were also calculated between the HRSD score, the Newcastle score, and the activity ratios of the depressed patients.

Results

The clinical characteristics of the patients and the controls are given in Tables I and II. The patients with MDD were older than both the control subjects and the patients with AD, but this difference was not significant. The sex ratio of the subjects in the depressed group was also different

TABLE I
Clinical characteristics of subjects

	Groups		
	MDD	*AD*	*Controls*
No. of subjects (no. of men)	18 (4)	14 (7)	12 (6)
Age range: years	66–90	54–81	58–91
Mean age (s.d.): years	77 (7.8)	72.3 (8.4)	74.7 (9.8)
MMS score			
range	20–30	6–19[1]	24–30
mean (s.d.)	27.3 (3.3)	11.9 (4.6)	29 (1.8)
CAMCOG score			
range	67–91[2]	5–63[1]	77–106
mean (s.d.)	83.1 (7.8)	34.4 (18.5)	94.5 (12.8)

1. Three patients with AD had marked aphasia, thus making their scores on MMS and CAMCOG unreliable.
2. The CAMCOG scores of seven subjects are not available.

TABLE II
Characteristics of the 18 depressed patients

Characteristic	
HDRS (17-item) score	
range	18–34
mean	25.9
s.d.	5.2
Newcastle score	
range	1–9
median	5
GMS/AGECAT diagnosis: no. of subjects	
"depressive neurosis, level 3"	5
"depressive neurosis, level 4"	4
"depressive psychosis, level 4"	9
Past history of depression: no of subjects	
present	7
absent	11

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from that in the other groups. Hence in the ANCOVA the gender and diagnostic groups were used as factors and age was a covariate. Gender and age effects were also 'partialled out' in estimations of correlation coefficients. All the patients with MDD had unipolar depression and were treated by the clinical team with tricyclic antidepressants and/or electroconvulsive therapy (ECT) purely on clinical grounds. The SPECT was performed in the depressed patients before any ECT they received as part of their treatment.

The results of the visual reports on the scans (Table III) showed that more MDD and AD patients showed impaired regional cerebral perfusion than control subjects. The relevance of SPECT in studying the cerebral changes in depression is illustrated by one patient with MDD, who showed no abnormality on CT scan (Fig. 1) but markedly impaired perfusion on SPECT (Plate V).

TABLE III
Number of subjects showing impaired regional perfusion on qualitative assessment of SPECT scans

Regions involved	*Healthy control subjects (n = 12)*	*Depressed patients (n = 18)*	*Alzheimer's disease patients (n = 14)*
Left frontal	1	6	12**
Left temporal	3	8	8
Left parietal	1	8	10*
Left occipital	0	5	6
Right frontal	1	7	12**
Right temporal	2	9	8
Right parietal	1	8	8
Right occipital	0	5	4
At least two cerebral regions	2	8	13**

*$P<0.025$, **$P<0.005$, χ^2 test.

The comparison of the uptake ratios across the groups is given in Table IV. The mean ratios in all the cerebral regions of the depressed patients were intermediate between those of the AD patients and the control subjects. The difference is statistically significant for the total and almost reaches the levels of significance in the left temporal and right parietal regions.

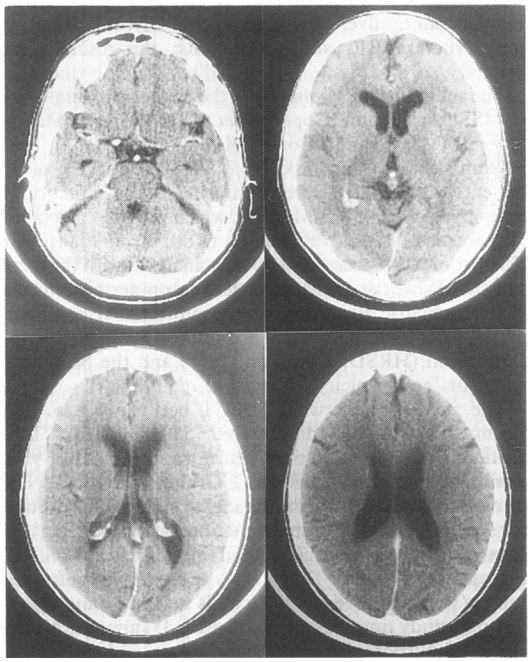


FIG. 1 A set of CT scans of a depressed patient, showing no abnormality. The SPECT scan of the same patient (Plate V) showed impaired cerebral perfusion.

TABLE IV
Analysis of covariance of the uptake ratios[1] showing the difference between the groups

Cerebral region	*Mean uptake ratios[1]*			F[2] *(for the main effect of group)*	P *value*
	Alzheimer patients (n = 14)	*Major depressives (n = 18)*	*Controls (n = 12)*		
Left occipital	0.94	0.97	1.00	1.97	0.15
Right occipital	0.93	0.98	1.00	3.01	0.06
Left temporal	0.87	0.92	0.95	3.20	0.05
Right temporal	0.87	0.91	0.94	2.29	0.11
Left parietal	0.83	0.87	0.90	1.87	0.17
Right parietal	0.81	0.86	0.89	3.23	0.05
Left frontal	0.76	0.78	0.85	2.97	0.06
Right frontal	0.73	0.76	0.81	2.65	0.08
Total	0.84	0.88	0.92	3.46	0.04

1. Uptake by the cerebral regions of interest:uptake by the cerebellum.
2. All F values are with 2 and 41 degrees of freedom. The F values for the main effect of gender, the interaction of the main effects and for the covariate were not significant.

https://doi.org/10.1192/S0007125000291873 Published online by Cambridge University Press

The partial correlation between the Newcastle score for 'endogenicity' in the depressed patients and the regional uptake ratio, controlling for age and gender, was found to be negative in all regions, but reached levels of significance in right and left occipital areas ($r = -0.64$ and -0.56, $P = 0.008$ and 0.024, respectively). The partial correlation between the HRSD scores of depressed patients and the regional uptake ratios was not significant in any of the cerebral regions, although it was negative for most areas, the highest correlation being in the right occipital region ($r = -0.31$, $P = 0.24$).

Analyses of covariance were also carried out to examine the difference in the rCBF parameter between those with and without a past history of depression, but no difference was found. Analysis of covariance was also carried out across the three groups of subjects to examine any differences in the left–right asymmetry of uptake ratios in the patients compared with the controls. The ratio of the differences between left and right regional uptake ratio and the sum of the left and right uptake ratio was used as an index of regional asymmetry in perfusion. Using age as a covariate, ANCOVA was carried out with group and gender as the main factors, because the lateral asymmetry in regional perfusion in females was more biased in favour of the left side, compared with the male subjects. No group difference in the lateral asymmetry in perfusion was found, but in the temporal area the main effect of gender was significant.

Discussion

The present study demonstrates regional cerebral perfusion impairments in elderly depressed patients, which is in keeping with the findings of a number of recent studies (Devous *et al*, 1984; Sackeim *et al*, 1990). Sackeim *et al* (1990) showed that the reduction in cerebral perfusion in major depression was similar in magnitude to that seen in AD (Prohovnik *et al*, 1988). Although the difference in the activity ratios between the groups in the present study failed to reach statistical significance, the trend is very strong. This could partly be due to the small sample size and the wide variation in the severity of dementia in AD patients. The method used in the study for assessment of cerebral perfusion is indirect and does not yield absolute values. However, this index of cerebral perfusion has been shown to be a valid measure, as the perfusion indices correspond to discrete neuropsychological deficits in patients with AD (Burns *et al*, 1989). Cerebral perfusion and glucose metabolism are tightly coupled on a local basis (Baron *et al*, 1982). While decoupling may occur in some neurological diseases there is no reason to suspect that this occurs in major depression.

The cause of the rCBF deficits in major depression is unknown. It is unlikely to have a primarily vascular origin, as the distribution of impaired perfusion shown by Sackeim *et al* (1990) does not conform to any topographical distribution of the major blood vessels in the brain. In our study, we specifically excluded individuals with significant vascular pathology. Hence this question of any possible relationship between vascular pathology and the impaired perfusion in the elderly depressed remains unanswered.

There are several lines of evidence suggesting cerebral changes in depression, particularly in the elderly. Apart from impaired cerebral perfusion, there are neurochemical and neuroanatomical changes in depressed patients, which are similar to those in patients with degenerative dementia (Seiver & Davis, 1985; Alexopoulous *et al*, 1988). Several clinical studies point towards an interface between depression and dementia in the elderly. Although earlier studies minimised the cognitive changes observed in depressive illness and treated them as instances of pseudodementia, many recent studies have confirmed that depression is not uncommon among patients with primary degenerative dementia, and many elderly depressed patients progress to established dementia (Reifler *et al*, 1982; Reding *et al*, 1985; Lazarus *et al*, 1987).

Pearlson *et al* (1989) reported the CT changes in two groups of elderly depressed subjects, one with cognitive decline severe enough to merit a diagnosis of dementia, and the other cognitively normal. Their findings suggest that these two groups differ in the extent of neuroanatomical abnormalities as measured by CT attenuation and ventricle:brain ratios (VBR). The CT values of the whole depressed group lay between those of AD patients and normal controls, but the CT values of depressed patients with dementia syndrome clustered near those of AD patients.

It is not yet clear whether the cerebral changes accompanying depressive illness are state dependent. There is some evidence that the cognitive impairment and the impairments in rCBF are not always completely reversible. Ventricular enlargement on the CT scan have been reported in young patients with affective disorders (Pearlson *et al*, 1984) and it is possible that the neuroanatomical changes shown on CT scan in depression are the result of irreversible structural abnormalities.

The prognostic implications of the cerebral changes in depression remain unclear. The similarities between the elderly depressed and AD patients suggest that the CT changes as well as the rCBF impairments of depression could well be precursors of a progressive dementing illness (Kral, 1983; Reding *et al*, 1985), but the study by Pearlson *et al* (1989) showed that on retesting after two years, all

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but one of the depressed patients presenting with a dementia syndrome when ill were free from cognitive decline. Moreover, reports of high rates of dementia on follow-up of depressed patients (Reding *et al*, 1985) were possibly biased in the sample selection so as to include many with neurological disorder, and the conclusions could not be extended to depressed patients in general. Hence the cerebral changes observed in depression may not directly point to a progression to degenerative dementia, at least in the short term. The prognostic implications of these changes can only be established by studies involving repeat measures and long-term follow-up.

This study also aimed to examine any possible relationship between severity or the nature of depression and the impairment in cerebral perfusion. No correlation was found between scores on HDRS and the indices of cerebral perfusion. The small sample size precludes a firm conclusion on the absence of correlation, but the study by Sackeim *et al* (1990) also failed to show any significant correlation. This study suggests that patients with endogenous depression are more likely to have impaired rCBF.

The prognostic implications of rCBF impairment in the elderly depressed are important not only for a better understanding of the pathophysiological basis of depression, but also in delineating subgroups of depressed patients. The patients of the present study are being followed up with a view to examining this issue.

Acknowledgements

We are grateful to Dr R. Philpot and Dr M. T. Malcolm for permission to study patients under their care, to Mr M. Dewey for advice on statistical analyses, and to Amersham International and the Human Ageing Trust for financial assistance.

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*A. K. Upadhyaya, *Department of Psychiatry*; M. T. Abou-Saleh, *Department of Psychiatry*; K. Wilson, *Department of Psychiatry*; S. J. Grime, *Department of Nuclear Medicine*; M. Critchley, *Department of Nuclear Medicine, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX*

*Correspondence

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