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Regional cerebral blood flow abnormalities in late-life depression: Relation to refractoriness and chronification

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Abstract We examined patterns of regional cerebral blood flow (rCBF) abnormalities in 18 patients with major depressive disorder in late life using single photon emission computed tomography (SPECT) and ^{99m}Tc-hexamethyl-propylenamine oxime (^{99m}Tc-HMPAO). Compared with 13 age-matched controls, relative rCBF was significantly decreased bilaterally in the anterior cingulate gyrus, the prefrontal cortex, the temporal cortex, the parietal cortex, the hippocampus and the caudate nucleus. However, it was not correlated with the severity of depression or global cognitive dysfunction. In 10 patients with a prolonged depressive episode or prolonged residual symptoms (the refractory subgroup), robust and extensive decreases in rCBF were found compared with controls and the rCBF decreased significantly in the anterior cingulate gyrus and the prefrontal cortex compared with that in the non-refractory subgroup. In the non-refractory subgroup, rCBF decreased significantly in the caudate nucleus and tended to decrease in the anterior cingulate gyrus compared with controls. These findings indicate that dysfunction of the limbic system, the cerebral association cortex and the caudate nucleus may be implicated in late-life depression and that robust and extensive hypoperfusion, especially in the anterior cingulate and the prefrontal regions, may relate to refractoriness or chronification of depression.

Key words anterior cingulate, chronification, late-life depression, prefrontal cortex, refractoriness, regional cerebral blood flow.

INTRODUCTION

Depression in late life is commonly characterized by severe psychomotor agitation or retardation, therapy resistance, sometimes with adverse reactions to medication, and high rates of chronicity with frequent recurrence. According to long-term follow-up studies, one-quarter to one-third of late-life depressed patients retain cognitive and emotional changes, even after the subsidence of severe depressive episodes.[1,2] Post referred to this as 'residual depressive invalidism', a distressing and fluctuating condition that predisposes to recurrence and produces enormous social difficulties for the patient and family.[1,3] Furthermore, it is suggested that late-life depression with reversible cognitive impairment may relate to the early stage of dementia.[4,5] Thus, depression in late life has been a peculiar category among the mood disorders and elucidation of the pathophysiology for refractoriness, chronification and reversible cognitive dysfunction may be central to improving the diagnosis and treatment of this disorder.

Recently, functional imaging techniques, such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), have been widely used to investigate brain function in depressive disorders. However, to our knowledge, few studies using neuroimaging techniques have targeted the refractoriness or chronification in the late-life depressive disorder. We investigated the pattern of regional cerebral blood flow (rCBF) abnormalities in late-life major depressive disorder using SPECT and ^{99m}Tc-labeled hexamethyl-propylenamine oxime (^{99m}Tc-HMPAO)[6,7] and also investigated its relation to various clinical parameters, including severity of depression, global cognitive dysfunction, refractoriness, and recurrence.

METHODS

Subjects and clinical evaluation

Eighteen patients with late-life depression (mean (±SD) age 66.2±7.3 years, range 50–77 years) were selected from the psychiatric service of Tohoku University Hospital. All patients had been diagnosed with major depressive disorder, single episode or recurrent, according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV),[8] for their most recent depressive episode during the period 1994–1996. Each patient was either in a major depressive episode or in a state of partial remission, as indicated by DSM-IV, at entry into the present study. Exclusion criteria were a past or present history of neurological or other psychiatric disorders, drug

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and/or alcohol abuse, significant previous or current medical illness, focal abnormality on X-ray CT scan, a score below 20 on the Mini-Mental State Examination (MMS)[9]or electroconvulsive therapy within the past 6 months. Patients on relatively low-dose anti-depressant medication were accepted into the study, except for those patients using cerebral metabolic activators, vasodilators or dopamine agonist medications (Table 1).

Thirteen age-matched healthy volunteers (mean age 66.4±7.8 years, range 54–77 years) who had no history of any kind of significant medical illness, neurological disorder or psychiatric illness were recruited from among local residents.

All subjects were right handed. The purpose and procedures of this clinical study were explained to all subjects and written informed consent was obtained from each subject in accordance with the Declaration of Human Rights, Helsinki 1975.

Just prior to the SPECT scan, all patients received clinical examinations using the 17 item Hamilton Rating Scale for Depression (HAM-D)[10] and MMS for global cognitive function. At the same time, the age at onset of the first depressive episode, the number of depressive episodes and the clinical course up to the SPECT study were retrospectively reviewed and patients were divided into two subgroups according to the following definitions: (i) refractory depression was defined as a prolonged major depressive episode or a prolonged partial remission that lasted for more than 1 year prior to the present study despite long-term anti-depressant medication in adequate doses (however, many patients were medicated in relatively low doses because of the intolerance of anti-depressants in the elderly); and (ii) non-refractory depression was defined as a major depressive episode or subsequent partial remission, that occurred within 1 year prior to the present study and that was preceded by a normal mental state.

Ten (mean age 69.2±6.2 years) and eight patients (mean age 62.5±6.9 years) met the criteria for refractory and non-refractory depression, respectively. Eight of 10 patients with refractory depression had HAM-D scores below 15 and were in a state of partial remission with prolonged residual symptoms as described by Post as 'depressive invalidism'.[1] They often complained of fatiguability, low volition and intiative, poor concentration and amnesia, insomnia and/or other neurasthenic physical symptoms occasionally combined with hypochondrical attitude, psychomotor slowing and a tendency towards a depressed mood and recurrence.

SPECT Scan

Single photon emission CT scans were obtained 5–10 min after an intravenous bolus injection of 925–1110 MBq ^{99m}Tc-HMPAO as a CBF tracer. During injection of ^{99m}Tc-HMPAO, subjects were lying in a supine position with their eyes closed. One SPECT scanner (SPECT-2000H; Hitachi Medico Corp., Tokyo, Japan),[11] a four-head rotating gamma camera with in-plane and axial resolutions of 8 mm full width at half maximum (FWHM), was used for all measurements. The SPECT scan protocol involved 64 projections at 20 s (20 s × four-head camera = total 80 s) per projection, with a 360° rotation of the camera. Image reconstruction was performed by filtered back projection using a Butterworth filter[12] and attenuation correction was made numerically by assuming an elliptic object shape for each slice and a uniform attenuation coefficient (0.1 /cm).[13,14] Correction for scattered photons

Table 1. Demographic and clinical characteristics

		Depression in late life		
	All patients	Refractory	Non-refractory	Controls
Number	18	10	8	13
Sex (M/F)	6/12	5/5	1/7	2/11
Age (years)*	66.2 ± 7.3	69.2 ± 6.2	62.5 ± 6.9	66.4 ± 7.8
Age at onset (years)*	61.2 ± 10.1	65.1 ± 6.1	56.5 ± 12.0	
No. episodes*	2.4 ± 2.1	2.1 ± 1.4	2.7 ± 2.8	
17-HAM-D*	13.7 ± 8.4	10.3 ± 5.1	16.0 ± 10.0	
MMS*	27.5 ± 2.8	27.7 ± 2.7	27.2 ± 2.8	
Medicated anti-depressants**				
Imipramine (30 mg)		0	1	
Clomipramine (75 mg)		1	2	
Amitriptyline (10–20 mg)		2	0	
Maprotiline (10–75 mg)		4	2	
Mianserin (10–30 mg)		3	0	
Dosulepin (25 mg)		1	0	
Setiptiline (3 mg)		0	2	
Trazodone (150 mg)		0	2	
Free		1	1	

17-HAM-D, 17 item Hamilton Rating Scale for depression; MMS, Mini-Mental State Examination. *Values are the mean ±SD; **values are the number of cases.

Two patients in the refractory subgroup and two patients in the non-refractory subgroup were medicated in combinations of two types of anti-depressants.

was not applied. Image slices were arranged parallel to the orbitomeatal (OM) line and obtained at 8 mm intervals in the whole brain. After the SPECT measurements, X-ray CT scans were obtained with the same slices as for SPECT images in all subjects.

Data analyses

The SPECT images for each subject were transferred to a Unix workstation TITAN-750, where data analyses were performed. Eight transaxial slices (16, 24, 40, 48, 64, 72, 80 and 88 mm above and parallel to the OM line) were selected for semiquantitative analyses. Anatomical structures of the brain in the SPECT images were identified with reference to the corresponding CT images in each subject and a human brain atlas.[15] Eighty-five regions of interest (ROI), circular and 16 mm in diameter, were manually and directly positioned on appropriately matched scans by visual inspection (Fig. 1). A relative rCBF ratio to cerebellum (rCBF/C) was calculated for each ROI using the average tissue activity in the region divided by the average tissue activity in the bilateral cerebellar hemispheres and vermis. Additionally, left/right ratios of rCBF/C (L/R) were calculated to evaluate the lateralization of rCBF.

Statistical intergroup comparisons were made using one-way analysis of variance (ANOVA) and, when significant differences were obtained, post hoc planned *t*-tests (unpaired) were performed for each ROI using Fisher's protected least-significant difference test. Correlations between rCBF and clinical parameters were tested using Spearman's rank correlation coefficient.

A P value below 0.05 was considered significant.

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of the subjects are summarized in Table 1. In depressed subjects, there was a significant positive correlation between age and age at onset of the first depressive episode ($r=0.91$; $P<0.01$). However, no correlations were found between age, number of episodes, HAM-D and MMS.

The mean age of the subjects in the refractory subgroup did not differ significantly from that in the non-refractory subgroup or the control group ($F_{[2,28]}=1.77$; $P=0.18$). Age at onset, number of episodes, 17-HAM-D and MMS were not statistically different between refractory and non-refractory subgroups, although the trend in the refractory subgroup was towards increment in the mean age at onset ($t=1.84$; $P=0.08$)

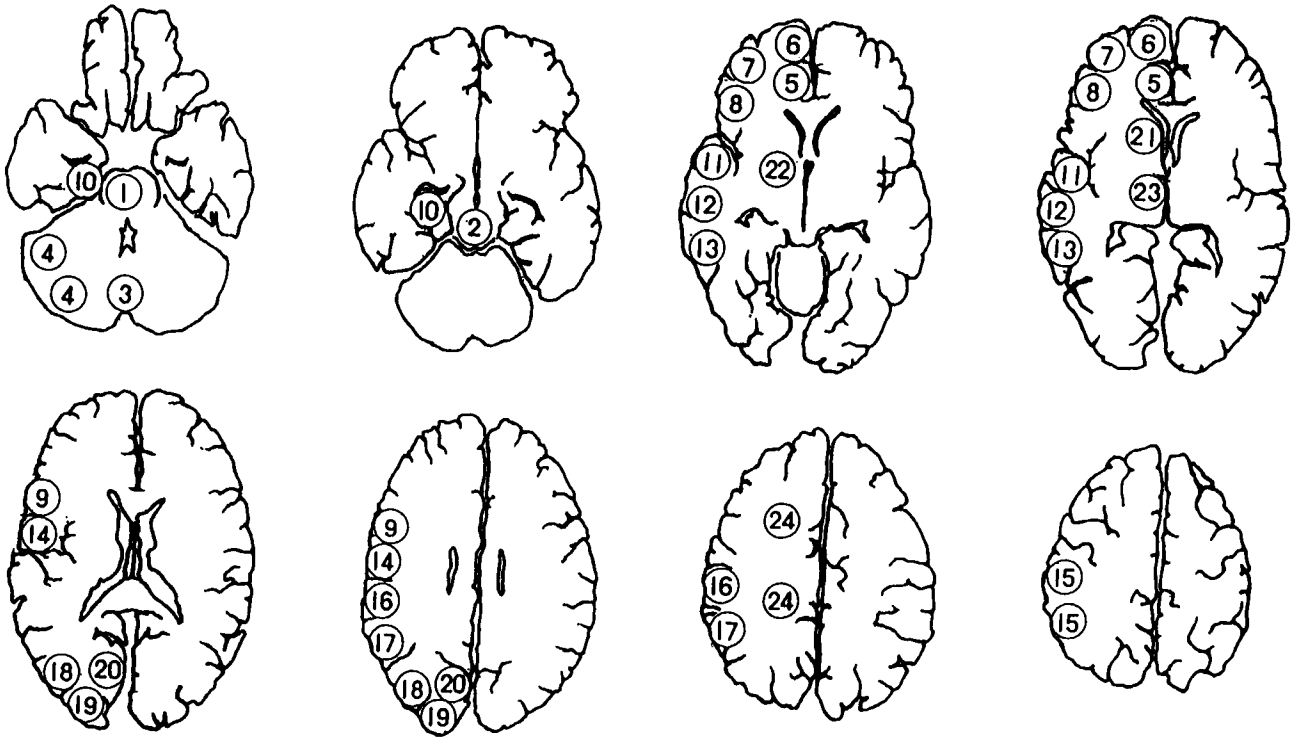

Figure 1. Location of regions of interest (ROIs) for semiquantitative analysis in relative regional cerebral blood flow (rCBF). The ROIs on the midline and the right hemispheric structures are numbered as follows: 1, pons; 2, midbrain; 3, cerebellar vermis; 4, cerebellar hemisphere; 5, anterior cingulate gyrus; 6, 7, 8, superior, middle, and inferior frontal gyri; 9, precentral gyrus; 10, hippocampal gyrus; 11, 12, 13, superior, middle, and inferior temporal gyri; 14, post central gyrus; 15, superior parietal lobule; 16, supramarginal gyrus; 17, angular gyrus; 18, 19, lateral and posterior areas of occipital lobe; 20, occipital cuneus; 21, caudate nucleus; 22, lentiform nucleus; 23, thalamus; 24, semiovale center. The ROIs on the left hemispheric structures were positioned symmetrically.

Table 2. Comparison of relative regional cerebral blood flow between patients with late-life depression and controls

Regions of interest	CBF/C		L/R	
	Depression	Control	Depression	Control
Pons	0.78 ± 0.06	0.80 ± 0.03		
Midbrain	0.79 ± 0.08	0.81 ± 0.05		
Cerebellar vermis	0.99 ± 0.03	0.98 ± 0.04		
Cerebellar hemisphere	0.99 ± 0.00	1.00 ± 0.00	0.97 ± 0.03	0.97 ± 0.02
Anterior cingulate gyrus	0.76 ± 0.06***	0.85 ± 0.05	0.97 ± 0.05	0.98 ± 0.03
Superior frontal gyrus	0.80 ± 0.06**	0.87 ± 0.05	1.00 ± 0.03	1.01 ± 0.03
Middle frontal gyrus	0.80 ± 0.06*	0.85 ± 0.04	0.98 ± 0.04	1.00 ± 0.03
Inferior frontal gyrus	0.79 ± 0.06*	0.85 ± 0.05	0.95 ± 0.04	0.96 ± 0.05
Precentral gyrus	0.79 ± 0.05	0.83 ± 0.04	0.96 ± 0.04	0.96 ± 0.04
Postcentral gyrus	0.78 ± 0.06*	0.83 ± 0.04	1.03 ± 0.05	1.04 ± 0.05
Hippocampal gyrus	0.74 ± 0.04*	0.78 ± 0.04	0.95 ± 0.04	0.95 ± 0.04
Superior temporal gyrus	0.81 ± 0.06**	0.87 ± 0.04	0.95 ± 0.06	0.95 ± 0.05
Middle temporal gyrus	0.84 ± 0.06	0.87 ± 0.03	0.95 ± 0.05	0.92 ± 0.03
Inferior temporal gyrus	0.79 ± 0.06*	0.83 ± 0.04	0.94 ± 0.03	0.94 ± 0.05
Superior parietal lobule	0.76 ± 0.08	0.80 ± 0.06	0.96 ± 0.07	0.96 ± 0.06
Supramarginal gyrus	0.80 ± 0.05*	0.86 ± 0.05	0.96 ± 0.05	0.95 ± 0.05
Angular gyrus	0.79 ± 0.05*	0.84 ± 0.04	0.98 ± 0.04	0.97 ± 0.05
Lateral area of occipital	0.78 ± 0.04	0.82 ± 0.07	0.96 ± 0.03	0.98 ± 0.05
Posterior area of occipital	0.79 ± 0.06	0.85 ± 0.08	0.96 ± 0.04	0.96 ± 0.03
Occipital cuneus	0.90 ± 0.04	0.93 ± 0.07	0.97 ± 0.05	0.98 ± 0.03
Caudate nucleus	0.85 ± 0.08**	0.95 ± 0.05	1.04 ± 0.06	1.03 ± 0.07
Lentiform nucleus	0.95 ± 0.08	0.97 ± 0.05	0.97 ± 0.03	0.99 ± 0.04
Thalamus	0.90 ± 0.07	0.94 ± 0.06	1.03 ± 0.05	1.01 ± 0.03
Semiovale center	0.68 ± 0.08	0.72 ± 0.07	0.96 ± 0.05	0.97 ± 0.08

CBF/C, relative regional cerebral blood flow ratio to cerebellum; L/R; left/right ratio of regional cerebral blood flow. Values are the mean ± SD. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

SPECT results

Significant rCBF reductions were found in the anterior cingulate gyrus, the prefrontal cortex (the superior, middle and inferior frontal gyri), the temporal cortex (the superior and inferior temporal gyri), the parietal cortex (the postcentral, supramarginal and angular gyri), the hippocampus and the caudate nucleus in depressed subjects compared with controls (Table 2). Of these regions, the greatest decrement was observed in the anterior cingulate, the superior frontal and the superior temporal gyri and the caudate nucleus. No significant lateralization was found in any region. There were no significant correlations between any clinical parameters (age, age at onset, number of episodes and HAM-D and MMS scores) and rCBF (Table 3).

In the refractory subgroup, robust and extensive rCBF reductions were found, especially in the anterior cerebral regions, when compared with controls and significant reductions were found in the anterior cingulate gyrus and the prefrontal cortex when compared with the non-refractory subgroup. In the non-refractory subgroup, significant rCBF reduction was found in the caudate nucleus and there was a trend towards decrement in the anterior cingulate gyrus ($t = -1.99$; $P = 0.06$) when compared with controls (Table 4). Magnetic resonance

Table 3. Correlations between clinical parameters and relative regional cerebral blood flow to cerebellum in late-life depression

	Age	Onset	Episode	HAM-D	MMS
ACIN	−0.30	−0.22	−0.00	0.41	0.38
PFRT	−0.11	−0.03	−0.40	0.19	0.18
CEN	−0.05	0.02	−0.35	0.19	0.42
TMP	−0.02	0.07	−0.36	0.12	0.30
HIP	−0.29	−0.22	−0.20	0.16	0.17
PPRT	0.00	0.00	−0.33	0.03	0.16
OCP	−0.07	−0.01	−0.39	0.01	0.11
CAD	−0.17	−0.24	0.16	0.05	0.29

Values are the Spearman's rank correlation coefficients.

ACIN, anterior cingulate gyrus; PFRT, CEN, TMP, prefrontal, central and temporal regions, respectively; HIP, hippocampal gyrus; PPRT, OCP, posterior parietal and occipital regions, respectively; CAD, caudate nucleus; Onset, age at onset; Episode, number of episodes; HAM-D, 17 item Hamilton Rating Scale for Depression; MMS, Mini-Mental State Examination.

No statistical significance was found in any correlations between clinical parameters and the relative regional cerebral blood flow ratio to cerebellum.

Table 4. Comparison of relative regional cerebral blood flow between patients with refractory and non-refractory late-life depression and controls

Regions of interest	Refractory	Non-refractory	Controls
Pons	0.78 ± 0.06	0.78 ± 0.05	0.08 ± 0.03
Midbrain	0.78 ± 0.04	0.80 ± 0.10	0.81 ± 0.05
Cerebellar vermis	0.99 ± 0.02	0.99 ± 0.04	0.98 ± 0.04
Cerebellar hemisphere	1.00 ± 0.00	0.99 ± 0.00	1.00 ± 0.00
Anterior cingulate gyrus	0.73 ± 0.05***†	0.80 ± 0.04	0.85 ± 0.05
Superior frontal gyrus	0.77 ± 0.04***†	0.84 ± 0.05	0.87 ± 0.05
Middle frontal gyrus	0.78 ± 0.06**	0.83 ± 0.05	0.85 ± 0.04
Inferior frontal gyrus	0.76 ± 0.05**†	0.83 ± 0.05	0.85 ± 0.05
Precentral gyrus	0.77 ± 0.04**	0.81 ± 0.06	0.83 ± 0.04
Postcentral gyrus	0.76 ± 0.05**	0.81 ± 0.05	0.83 ± 0.04
Hippocampal gyrus	0.73 ± 0.06*	0.76 ± 0.03	0.78 ± 0.04
Superior temporal gyrus	0.79 ± 0.06**	0.83 ± 0.06	0.87 ± 0.04
Middle temporal gyrus	0.83 ± 0.06*	0.85 ± 0.06	0.87 ± 0.03
Inferior temporal gyrus	0.78 ± 0.05*	0.80 ± 0.05	0.83 ± 0.04
Superior parietal lobule	0.77 ± 0.04	0.75 ± 0.11	0.80 ± 0.06
Supramarginal gyrus	0.79 ± 0.05**	0.82 ± 0.05	0.86 ± 0.05
Angular gyrus	0.79 ± 0.04*	0.79 ± 0.06	0.84 ± 0.04
Lateral area of occipital	0.77 ± 0.03	0.80 ± 0.04	0.82 ± 0.07
Posterior area of occipital	0.77 ± 0.06*	0.83 ± 0.06	0.85 ± 0.08
Occipital cuneus	0.89 ± 0.04	0.91 ± 0.05	0.93 ± 0.07
Caudate nucleus	0.85 ± 0.07**	0.86 ± 0.10*	0.95 ± 0.05
Lentiform nucleus	0.93 ± 0.08	0.97 ± 0.08	0.97 ± 0.05
Thalamus	0.89 ± 0.06	0.92 ± 0.07	0.94 ± 0.06
Semiovale center	0.67 ± 0.07	0.69 ± 0.93	0.72 ± 0.07

Values are the mean ± SD ^{99m}Tc uptake ratios to cerebellum (CBF/C). ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$ compared with control; †$P < 0.05$ compared with non-refractory depression.

imaging (MRI) and SPECT scans from a patient with refractory late-life depression are shown in Fig. 2.

DISCUSSION

A conspicuous finding in the present study was significant cerebral hypoperfusion in the anterior cingulate gyrus, the prefrontal cortex, the temporal cortex, the parietal cortex, the hippocampus and the caudate nucleus in patients with late-life depression in resting conditions compared with controls. These findings cannot be simply compared with previous reports[16–32] because of the differences in types of depression, diagnostic criteria, subject ages, radiotracers and procedures for data analyses. However, many SPECT studies have described rCBF abnormalities in different types of depression (Tables 5, 6).

Of these reports, our findings are consistent with those of Mayberg *et al.*[27] and Curran *et al.*[30] Mayberg *et al.* studied relatively younger subjects with unipolar refractory depression using ^{99m}Tc-HMPAO SPECT and demonstrated hypoperfusion in the anterior cingulate, the frontal, the anterior temporal and the caudate regions.[27] Curran *et al.* studied older depressed subjects using ^{99m}Tc-exametazime and found rCBF reduction

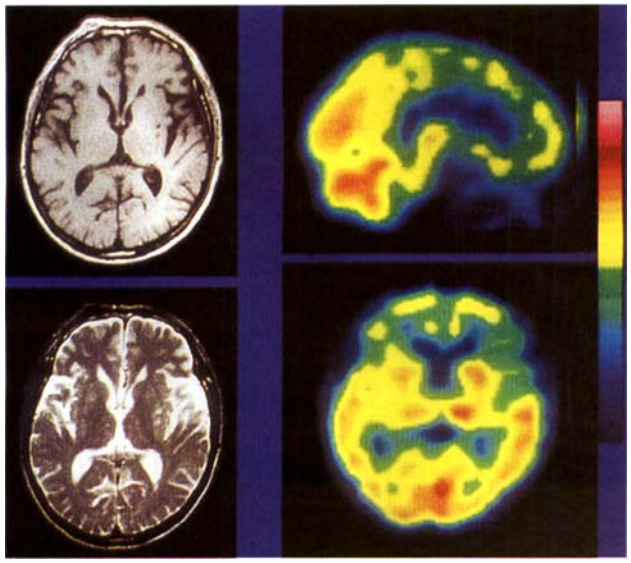

Figure 2. Magnetic resonance image (MRI) and single photon emission computed tomographic (SPECT) scans from a 67-year-old male patient with refractory recurrent major depressive disorder. The MRIs show small lesions of suspected lacunar infarctions in the left basal ganglia and mild atrophy of the left temporal lobe. Otherwise almost normal findings (top, T1 weighted images; bottom, T2 weighted images) were noted. The SPECT images demonstrate gross hypoperfusion in the bilateral anterior cingulate and prefrontal regions (top, sagittal images; lower, axial images). In the axial MRI and SPECT images the subjects' right is on the left in the figure.

Table 5. Summary of the single photon emission computed tomography studies on cerebral blood flow in depression

Reference	Radiotracer	Patients* No.	Controls* No.	CBF at rest compared with control	Clinical correlation with HAM-D score
Mathew *et al.*[16]	^{133}Xe	13 (30.07 ± 7.33)	13	Reduction in left hemisphere	Negative correlation
Uytdenhoef *et al.*[17]	^{133}Xe	16 (51.5 ± 13.4)	20 (41 ± 11)	Left frontal hypervascularization and right posterior hypovascularization	–
Gur *et al.*[18]	^{133}Xe	14 (31.0 ± 9.28)	25 (27.49 ± 10.96)	No significant difference	No correlation
Silfverskiöld and Risberg.[19]	^{133}Xe	31 (56.0 ± 12.0)	31 (55.3 ± 11.4)	No significant difference	–
Schlegel *et al.*[20]	^{195m}Au	21 (45.9 ± 13.2)	21 (30.7 ± 8.4)	Reduction in right global, frontal, parietal, occipital and temporal and left global and frontal regions	Negative correlation
Sackeim *et al.*[21]	^{133}Xe	41 (60.24 ± 12.02)	40 (60.68 ± 10.68)	Reduction in selective frontal, central, superior temporal and anterior parietal regions	Negative correlation
Kanaya and Yonekawa[22]	^{123}IMP	32 (53.5)	20 (35.7)	Reduction in all over the cerebral regions, especially lower rCBF in left hemisphere	Negative correlation
Delvenne *et al.*[23]	^{133}Xe	38 (39.3 ± 13.1)	16 (44.7 ± 24.2)	Reduction in left hemisphere in bipolar and endogenous depression	–
Amsterdam *et al.*[24]	^{131}IMP	19 (41 ± 11)	12 (37 ± 16)	Temporal lobe asymmetry	–
Austin *et al.*[25]	^{99m}Tc-exametazime	40 (45.8 ± 13.7)	20 (47.2 ± 15.1)	Reduction in the majority of cortical and subcortical regions and most significantly in temporal, inferior frontal and parietal regions	Negative correlation
Yazici *et al.*[26]	^{99m}Tc-HMPAO	14 (33.5 ± 2.7)	10 (33.3 ± 2.6)	Reduction in bilateral temporal regions and lower L/R ratio of the prefrontal region	Negative correlation
Mayberg *et al.*[27]	^{99m}Tc-HMPAO	13 (42 ± 11)	11 (35 ± 13)	Reduction in frontal and anterior temporal cortex, anterior cingulate and caudate	No correlation

*Data show the number of patients with the mean (± SD) patient age given in parentheses.
rCBF, regional cerebral blood flow; L/R, left/right ratio of rCBF.

in the anterior cingulate, the frontal, the temporal, the caudate and the thalamic regions in men only.[30] In addition, our findings confirm several previous PET findings of 'hypofrontality'[33–39] and low metabolic rate in the basal ganglia[34] in depression. The most reproducible finding is hypoperfusion or hypometabolism in the anterior and paralimbic brain regions, as previously indicated by Bench *et al.*[40] Our present study reconfirmed this finding and implicated hypoperfusion in the limbic system, the cerebral association cortex and the caudate nucleus in late-life depression.

Regarding the correlation between clinical symptoms and rCBF, the reported findings are inconsistent: a negative correlation between HAM-D scores and rCBF has been reported by some authors,[16,20–22,25,26] and no correlation has been reported by others.[18,27,29,31] Mayberg *et al.*[27] reported a significant association between psychomotor slowing and hypoperfusion in frontal and anterior cingulate regions. Curran *et al.*[30] also found a significant relationship between cognitive impairment indicated by the trial-making test B,[41] which mainly reflects attention and psychomotor speed, and hypoperfusion in the anterior cingulate, prefrontal, temporal and thalamic regions. In PET studies, Bench *et al.*[39] reported a relationship between global cognitive impairment indicated by MMS and rCBF reduction in the left medial prefrontal cortex. However, in the present study neither the symptom severity, indicated by HAM-D, nor the global cognitive dysfunction, indicated by MMS, was correlated with CBF in any regions. This finding indicates that symptom severity and global cognitive function in late-life depression may not simply relate to focal CBF reductions.

We have already demonstrated hypoperfusion in the limbic system and prefrontal cortex in both unipolar and bipolar

Table 6. Summary of single photon emission computed tomography studies on cerebral blood flow in late-life depression

Reference	Radiotracer	Patients* No.	Controls No.	CBF at rest compared with controls	Clinical correlation with HAM-D score
Gustafson *et al.* [28]	^{133}Xe	19 (60.0 ± 14)	22 (28.0 ± 7.3)	No significant difference	–
Upadhaya *et al.*[29]	^{99m}Tc-HMPAO	18 (77 ± 7.8)	12 (74.7 ± 9.8)	Intermediate reduction in total flow between in Alzheimer disease patients and in control subjects	No correlation
Curran *et al.*[30]	^{99m}Tc-exametazime	20 (70 ± 6.3)	30 (67.1 ± 6.2)	Reduction in anterior cingulate, temporal and frontal cortex and in caudate and thalamus in men only	–
Lesser *et al.*[31]	^{99m}Tc-HMPAO ^{133}Xe	39 (60.9 ± 8.1)	20 (69.1 ± 6.5)	Reduction in global flow, orbital frontal and inferior temporal regions	No clear correlation
Ito *et al.*[32]	^{99m}Tc-HMPAO	Unipolar: 11 (66.6 ± 7.1) Bipolar: 6 (66.7 ± 5.8)	9 (65.7 ± 10.5)	Reduction in prefrontal cortices, limbic systems and paralimbic areas in both depression groups	–
Present study	^{99m}Tc-HMPAO	18 (66.2 ± 7.3)	13 (66.4 ± 7.8)	Reduction in anterior cingulate gyrus, prefrontal cortex, temporal cortex, parietal cortex, hippocampus and caudate nucleus.	No correlation

Data show the number of patients with the mean (± SD) patient age given in parentheses.
CBF, cerebral blood flow.

refractory late-life depression using SPECT with anatomical standardization technique.[32] Our present study, based on ROI analyses, demonstrates the robust and extensive hypoperfusion, especially in the anterior cingulate and prefrontal regions, in refractory late-life major depressive disorder compared with controls and non-refractory depression. This finding indicates that reductions in rCBF in these regions may relate to refractoriness, chronification and prolonged residual symptoms, such as emotional lability, low volition and initiative, psychomotor slowing and mild cognitive impairment, rather than to symptom severity of depression indicated by HAM-D scores.

The cingulate region and its connection with the hippocampus and amygdala are main components of the limbic system implicated in the expression and modulation of emotion.[42,43] In particular, the anterior cingulate gyrus appears to be crucial for the emotional control of visceral, skeletal and endocrine flow,[44] initiation, motivation, goal-directed behaviors[45] and Posner's 'executive attention'.[46] The anterior cingulate and prefrontal cortices have connections with the striatum, making a series of parallel frontal-subcortical circuits.[47–49] Dysfunction in these circuits may cause behavioral syndromes, including depression, executive function deficits and apathy.[50,51] The prefrontal and temporoparietal association cortices form a parallel distributed network with strong limbic and paralimbic connectivities subserving arousal, attentional and motivational functions, as well as integrative and representational cognitive activities.[52,53] Thus, functional abnormalities in the limbic system, cerebral association cortex and caudate nucleus may be reciprocally interrelated and implicated in emotional, motivational, psychomotor and cognitive impairments of late-life depression, particularly in the refractory residual state.

The causes of rCBF changes in late-life depression are speculated to be varied. Some examples include effects of anti-depressant medications, neurochemical changes underlying depressive episodes, aging and insidious onset of organic brain disease, including early stages of the dementing disorder.

In the present study, depressed subjects were treated with relatively low doses of anti-depressants to prevent anticholinergic side effects, so that the effects of anti-depressant medication on rCBF would be minimal. Several previous studies[40,54–56] that reported improvement in rCBF abnormalities after recovery from depression suggest that the main source of rCBF changes may relate to underlying neurochemical changes during the depressive episodes. However, this cannot be discussed here because of a lack of data from longitudinal CBF analyses. With regard to the aging effects on rCBF abnormalities, several PET studies[57–60] have reported a significant association between age and rCBF or metabolic reduction in limbic, paralimbic and association cortices. These

aging effects may have exaggerated the pattern of rCBF abnormalities in late-life depression.

Finally, several recent follow-up studies[4,5] have suggested that a high proportion of late-life depressed patients with reversible cognitive impairment will be affected with true dementing disorder in the long term. Thus, the rCBF abnormalities in a proportion of refractory patients in the present study may be possibly due to an insidious organic brain disease, which would manifest as dementia in the future. Longitudinal follow-up SPECT studies should be performed to investigate the cause of rCBF abnormalities and to improve the management of late-life depressive disorder.

CONCLUSIONS

Our study of the patterns of rCBF abnormalities in late-life major depressive disorder using SPECT and ^{99m}Tc-HMPAO revealed significant rCBF reductions in the anterior cingulate gyrus, the prefrontal cortex, the temporal cortex, the parietal cortex, the hippocampus and the caudate nucleus. Neither the severity of depression nor the global cognitive dysfunction correlated with rCBF. In the refractory subgroup, robust and extensive rCBF reductions were observed, especially in the anterior cingulate gyrus and the prefrontal cortex. These findings indicate that dysfunction in the limbic system, the cerebral association cortex and the caudate nucleus may be implicated in late-life depression and that robust and extensive rCBF reductions, especially in the anterior cingulate and the prefrontal regions, may relate to refractoriness and chronification of depressive disorder.

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