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Qualitative magnetic resonance imaging findings in geriatric depression. Possible link between later-onset depression and Alzheimer's disease?

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ABSTRACT

Background. Several clinical and neuroimaging investigations support the notion that underlying brain changes may relate to depression in older patients, especially those with a later-age initial episode. However uncertainty still exists about diagnostic and pathogenic significance of structural brain abnormalities in aged depressives, in part because many studies lack all-elderly and age-similar normal comparison populations.

Methods. Brain morphology of elderly depressives ($N = 30$) and normal controls ($N = 36$) was compared by assessing magnetic resonance imaging (MRI) brain scans with qualitative criteria-based scales. Ratings included lateral and third ventricle enlargement, and cortical, medial temporal, and caudate atrophy.

Results. Significant differences between depressed and control groups were not demonstrated. Later-onset depressives had significantly more left medial temporal and left caudate atrophy than early-onset counterparts of similar age. Medial temporal atrophy significantly correlated with cognitive impairment and was not related to physical illness. Depressives with medial temporal atrophy ($N = 7$) were older and had later age at onset of depression than those without such changes. Cerebrovascular disease risk factors did not predict MRI abnormalities.

Conclusions. Results indicate non-specificity and lack of homogeneity of qualitatively measured structural brain changes in geriatric depression, but suggest that pathology of specific, lateralized brain regions may be implicated in some later-onset patients. The relationship between medial temporal atrophy and late-onset depression raises the possibility that such patients may suffer from as-yet undeclared Alzheimer's disease. Lack of association between cerebrovascular disease risk factors and brain changes suggests other pathophysiological contributions.

INTRODUCTION

Diverse clinical studies in geriatric psychiatry provide indirect support for the notion that depression in the elderly may be related to underlying brain pathology. For example, reversible cognitive impairment preferentially complicates major depression in patients over the age of 60 years (Folstein & McHugh, 1978). Depression in the elderly is often chronic, with approximately two-thirds of patients not sustaining a long-term lasting recovery (Post, 1972; Murphy, 1983), with some investigations additionally suggesting that depression may be a harbinger of irreversible dementia (Kral & Emery, 1989; Alexopoulos *et al.* 1993). Furthermore, major depression in the elderly is

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associated with an increased mortality (Rovner *et al.* 1991), which may be linked to brain cortical atrophy and ventricular enlargement (Jacoby *et al.* 1981). These reports have contributed to *in vivo* searches for structural brain correlates of depression in the elderly.

Several CT and MRI studies of ventricular/sulcal enlargement and/or cortical atrophy have demonstrated greater changes in middle-aged and older depressives as compared with age-matched controls (Dolan *et al.* 1985; Pearlson *et al.* 1989; Zubenko *et al.* 1990; Beats *et al.* 1991; Rabins *et al.* 1991; Wurthmann *et al.* 1992; Coffey *et al.* 1993). Furthermore, as compared with normals, middle-aged and older depressives have been found to have increased severity/frequency of signal hyperintensities on intermediate and T2 weighted MR images (Zubenko *et al.* 1990; Rabins *et al.* 1991; Coffey *et al.* 1990, 1993; Lesser *et al.* 1991; Brown *et al.* 1992), reductions in the volumes of basal ganglia structures (putamen and caudate) (Husain *et al.* 1991; Krishnan *et al.* 1992) and the frontal lobe (Coffey *et al.* 1993) as measured by MRI quantitative methods. Many neuroimaging studies in middle-aged and geriatric depressed patients also suggest that later-onset of first depressive episode may be associated with evidence of structural brain abnormalities (Jacoby & Levy, 1980; Shima *et al.* 1984; Krishnan *et al.* 1988; Coffey *et al.* 1988, 1989; Figiel *et al.* 1991; Lesser *et al.* 1991; Rabins *et al.* 1991; Alexopoulos *et al.* 1992; Fujikawa *et al.* 1993; Miller *et al.* 1994).

Despite a burgeoning interest in neuroimaging correlates in geriatric psychiatry, only a limited number of studies with age-matched controls actually exists in specifically elderly-only depressed populations, hence inconsistencies and questions still remain about the pathogenic, diagnostic, and clinical significance of structural brain changes. As such, this study extends MRI neuroimaging investigation of structural brain correlates of geriatric depression and represents an initial qualitative analysis of ventricular enlargement and cortical and subcortical atrophy in a developing series of elderly depressives and age-matched normal controls. This level of qualitative assessment serves as an inexpensive methodology to rate severity of structural brain changes systematically and additionally provides neuroanatomical direction for future more automated quantitative studies of these populations.

METHOD

MRI procedures

MR image acquisition

Subjects were scanned on one 1.0-tesla whole-body MRI system (Siemens Magnetom) with a dedicated head coil. The head position was orientated in the scanner via laser light sources fixed to the canthomeatal line, and was stabilized during the procedure by manufacturer-supplied foam head supports and velcro straps. Brain images were obtained in the coronal plane through the whole head in 3·1 mm contiguous slices by using a 50 degree FLASH (fast low angle shot) sequence with a repetition time (TR) of 40 ms and an echo time (TE) of 15 ms in one acquisition. This sequence provided 63 contiguous slices in a 256×256-pixel matrix with no zoom factor and a resolution of $1{\cdot}0 \times 1{\cdot}0 \times 3{\cdot}1$ mm in 11 min. A T2 weighted and proton-density (intermediate) series were also acquired in the axial plane for routine clinical evaluation of patients. This series had a repetition time (TR) of 2500 ms and an echo delay time (TE) of 25 and 90 ms. This sequence provided 20 parallel sections in a 256×256 matrix with a 1·3 zoom factor. Axial images were 7 mm thick with a 0·7 mm gap between each section.

Qualitative MRI scan analysis

Video-field hard copies were printed for visual qualitative evaluation. MRI scans of patients and comparison subjects were combined in a randomized order and evaluated independently, under blind conditions, by a research psychiatrist (B.B.) expert in neuroanatomy and neuroradiological assessment. On the coronal spin-lattice relaxation time (T1-weighted) scans, the following aspects of brain morphology were assessed: right and left lateral ventricle enlargement, third ventricle enlargement, right and left global cortical atrophy, right and left medial temporal structure atrophy (size and shape of hippocampus, amygdala, and parahippocampal gyrus, and temporal horn enlargement), and right and left caudate atrophy. Qualitative evaluations were made on the basis of 4-point scales (normal to severe). The criteria that were developed to classify regions of interest

on this scale have been explicated and employed in an earlier report from the Hillside neuroimaging centre (Lieberman *et al*. 1992) and are described in Appendix 1. Since severe pathology can exist in an older population, additional 'extreme' rating criteria (i.e. a rating of 'three') were added.

To assess the reliability of the MRI measurements, 15 brains (random mixture of depressed and control subjects) were measured by a second rater who was blind to subject category. Intraclass correlation values for inter-rater reliability for brain regions of interest were as follows: lateral ventricles (right = 0·91, left = 0·92); third ventricle (0·91); cortical atrophy (right = 0·84, left = 0·84); medial temporal atrophy (right = 0·91, left = 0·94); caudate (right = 0·73; left = 0·70).

Clinical procedures

Subjects

Thirty geriatric depressed patients that met inclusion/exclusion criteria were consecutively recruited from the Geriatric Psychiatry Service (in-patient units ($N = 14$), day hospital ($N = 6$), out-patient clinic ($N = 10$)) at Hillside Hospital, psychiatric division of Long Island Jewish Medical Center. Thirty-six normal controls were solicited via advertisement in local papers or by word-of-mouth (relatives of hospital personnel). Right-handedness was a study entry criterion for both groups. All subjects received a Structured Clinical Interview for DSM-III-R (SCID) (Spitzer *et al*. 1988). Patients met the following inclusion criteria: DSM-III-R (APA, 1987) diagnosis of major depression, unipolar as determined by a SCID; aged 65 years or over; and Hamilton Depression Rating Scale (Hamilton, 1960) score greater than or equal to 18. Exclusion criteria for patients and controls were assessed by two investigators (E.K.G. and P.A.) utilizing a standardized format for information collection and included: presence of a cardiac pacemaker, metallic clips, or other bodily metallic implants or artefacts because of the MRI procedure; significant acute medical illness or exacerbation of a chronic medical condition; presence of a neurodegenerative or any other brain disease/disorder (including Alzheimer's disease or a related dementia) (subjects did not meet DSM-III-R criteria for dementia or have a history of or present evidence suggesting Parkinson's disease, Huntington's disease, etc.); history of transient ischaemic attack (TIA) or stroke; and other past or current DSM-III-R diagnosis (for controls this included affective disorders). After complete description of the study to the subjects, written informed consent was obtained.

The following clinical information and rating scales were collected for all subjects: Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960); Clinical Global Impression (CGI) for depression (Guy, 1976); Folstein Mini-Mental State Exam (MMSE) (Folstein *et al*. 1975); extended Mini-Mental State Exam (Teng & Chui, 1987); age at onset of first depressive episode and number of past depressive episodes (admission to a psychiatric hospital or contact with a health care professional for evaluation and treatment of sustained depressive symptoms constituted an 'episode' of depression) and further subclassification of depression as early onset (EO) ($\leqslant 60$ years) or late onset (LO) (> 60 years) (Post, 1962; Greenwald & Kramer-Ginsberg, 1988; Burvill *et al*. 1989; Figiel *et al*. 1991); global physical illness rating scale of the Duke Older American Resources and Services (OARS) methodology (Duke University Center for the Study of Aging and Human Development, 1978); the Edinburgh Inventory for handedness (Oldfield, 1971); the modified Hachinski ischaemia scale (Rosen *et al*. 1980); history or presence of the following cerebrovascular risk factors: hypertension, diabetes mellitus, coronary artery disease, and smoking; and level of education achieved. Psychiatric ratings (HDRS, CGI) were completed by an experienced geriatric psychologist (E.K.G.), with demonstrated high interrater reliability (Greenwald & Kramer-Ginsberg, 1988). Other clinical/medical data were assessed (E.K.G., P.A.) utilizing a standardized format for information collection.

Part of one depressed patient's MRI scan series could not be rated secondary to motion artefact, and extended MMSE's were unable to be completed in eight depressed patients.

Statistical analyses

Depressed *versus* control group clinical comparisons were made using independent univariate t tests. When assumptions of homogeneity of variance were not realized, t tests

that used the 'standard' estimate error of variance and associated reduced degrees of freedom were used. Because visual atrophy ratings represent categorical data, differences between depressed and control groups were assessed by non-parametric tests (Mann–Whitney *U* test, chi-square test). The Pearson Product-Moment Correlation Coefficient was used to establish correlations between clinical/demographic and MRI variables. Similar parametric and non-parametric statistical methods were applied in comparisons between early- and late-onset depressive groups. Analysis of covariance procedures were also employed when relevant. Multiple regression linear techniques were used to estimate the effect of cerebrovascular disease predictors (hypertension, diabetes, coronary artery disease, and smoking) on MRI ratings. All reported *P* values reflect two-tailed tests.

RESULTS

Depressed and control groups were compared on clinical and demographic variables (see Table 1). Depressed patients were distinguished by lower education level and performance on cognitive ratings, and worse physical health ratings. Qualitative MRI ratings did not reveal significant differences between elderly depressed and control groups in any brain region assessed. The number of subjects in each group were sufficient to ensure that a type II statistical error would occur with less than a 20% probability (i.e. power = 0·80). When the depressed group was divided into early-onset (EO) and late-onset (LO) categories, no differences in current age or other clinical/demographic ratings were found, with the obvious exception of age at onset of first depressive episode (EO: $45{\cdot}7 \pm 14{\cdot}1$ years *v.* LO: $73{\cdot}2 \pm 3{\cdot}7$ years). However, when early-onset and late-onset depressed patients were compared on MRI ratings, late-onset patients had greater abnormalities, reaching statistical significance in the left caudate (Mann–Whitney *U* test: $z = -2{\cdot}06$, $P < 0{\cdot}04$) and left medial temporal region ($z = -2{\cdot}05$, $P < 0{\cdot}05$). In these regions of special interest, the proportion of early-onset and late-onset patients and controls with normal to severe atrophy ratings are presented in Table 2. In general, in these brain areas, late-onset depressives had greater evidence of structural changes, especially in the more severe ratings, than early-onset patients or controls, although differences between groups in distribution of rating categories did not reach statistical significance.

Table 1. *Clinical/demographic characteristics of depressed and control subjects*

Characteristic	Depressed ($N = 30$) Mean	s.d.	Controls ($N = 36$) Mean	s.d.	*P*
Age (years)	75·9	6·7	72·8	6·6	0·07
Education (years)	11·6	2·8	13·4	2·0	0·05
No. of past episodes	1·8	1·5	—	—	—
Modified Hachinski Ischaemic Score	0·6	0·6	0·1	0·23	< 0·0001
Mini-Mental State Exam	28·3	2·4	29·4	0·81	< 0·01
Extended Mini-Mental State Exam	90·2	8·9	96·6	2·8	< 0·0001
Global Physical Illness Rating Scale	3·4	0·7	1·7	0·7	< 0·0001
Hamilton Depression Rating Scale	25·6	4·9	1·3	1·7	< 0·0001
Clinical Global Impression for depression	4·5	0·5	1·0	0·2	< 0·0001
	Percentage distribution				
	N	%	*N*	%	*P*
Sex distribution					
Male	12	40	18	50	0·57*
Female	15	50	18	50	
Cerebrovascular risk factors					
Hypertension	11	37	12	33	0·98*
Coronary artery disease	6	20	2	6	0·16*
Diabetes mellitus	2	7	1	3	0·87*
Current smoker	1	3	2	6	1·00*

* Derived from chi-squared test.

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Table 2. *Percentage distribution of qualitative MRI ratings of caudate and medial temporal structures in early and late onset depressed patients and normal comparison subjects**

Brain region	Depressed patients: Early onset $N = 10$ (%)	Depressed patients: Late onset $N = 20$ (%)	Controls $N = 36$ (%)
Right medial temporal atrophy			
No abnormality (rating = 0)	80	52	83
Slight abnormality (rating = 1)	10	16	3
Moderate abnormality (rating = 2)	10	16	8
Severe abnormality (rating = 3)	0	16	6
Left medial temporal atrophy			
No abnormality	90	53	78
Slight abnormality	10	21	11
Moderate abnormality	0	10	8
Severe abnormality	0	16	3
Right caudate atrophy			
No abnormality	70	42	69
Slight abnormality	10	37	28
Moderate abnormality	20	21	3
Severe abnormality	0	0	0
Left caudate atrophy			
No abnormality	80	42	69
Slight abnormality	20	37	28
Moderate abnormality	0	21	3
Severe abnormality	0	0	0

* No significant difference in percentage distribution by chi-square.

In the depressed group, correlational analyses (see Table 3) revealed significant relationships between the extended MMSE and medial temporal and third ventricle ratings; and between right ventricular enlargement and the standard MMSE. No MRI ratings correlated with the modified Hachinski ischaemic score. All MRI ratings except medial temporal atrophy scores significantly correlated with global assessment of physical illness. Age, cognitive and physical health ratings were not significantly correlated with any MRI measure in the control population. Positive findings should be considered preliminary since multiple statistical comparisons were not controlled for. In the multiple regression models for MRI ratings, no relationships were observed between cerebrovascular risk factors and brain changes for depressed patients, control subjects, and the total group.

Depressed patients with medial temporal atrophy ratings $\geqslant 2$ ($N = 7$ (23%)) were significantly older ($80{\cdot}9 \pm 7{\cdot}5$ years *v.* $74{\cdot}5 \pm 5{\cdot}8$; $P = 0{\cdot}03$) and had non-significantly older age-at-onset ($71{\cdot}3 \pm 10$ *v.* $61{\cdot}4 \pm 16$ years) than depressed patients without such changes. Extended MMSE scores (available in only four of the seven patients with medial temporal atrophy) were also significantly worse in the group with medial temporal atrophy ($81{\cdot}4 \pm 12{\cdot}5$ *v.* $92{\cdot}8 \pm 5{\cdot}8$; $P = 0{\cdot}008$), even when age was covaried ($P < 0{\cdot}04$).

DISCUSSION

This study demonstrates the lack of homogeneity and non-specificity of structural brain changes assessed qualitatively in geriatric depression.

Table 3. *Correlation matrix of clinical/demographic variables and MRI ratings for the depressed group* ($N = 30$)

	Clinical/demographic variables and MRI ratings: Age	MMSE[a]	3MS[b]	No. episodes[c]	OARS[d]	Hach[e]	Age onset[f]	HDRS[g]	CGI[h]
Right ventricular enlargement	0·20	−0·41**	−0·32	−0·06	0·47**	0·04	0·14	0·13	0·01
Left ventricular enlargement	0·19	−0·06	−0·36	−0·09	0·49**	−0·14	0·26	0·11	−0·13
3rd ventricular enlargement	0·36	−0·28	−0·50*	−0·08	0·38*	0·03	0·29	0·15	−0·00
Right cortical atrophy	0·07	0·11	0·19	−0·17	0·44*	0·06	−0·02	−0·17	−0·28
Left cortical atrophy	0·07	0·11	0·19	−0·17	0·44*	0·06	−0·02	−0·17	−0·28
Right medial temporal atrophy	0·40*	−0·21	−0·50*	−0·20	0·32	0·14	0·28	0·07	0·03
Left medial temporal atrophy	0·19	−0·25	−0·55**	−0·27	0·30	0·08	0·33	−0·02	−0·07
Right basal ganglia size	0·21	−0·09	−0·11	−0·12	0·57**	0·16	0·01	0·17	0·16
Left basal ganglia size	0·16	0·20	−0·11	0·00	0·51**	−0·07	0·29	−0·00	0·03

[a] Mini-Mental State Exam; [b] Extended Mini-Mental State Exam; [c] Number of past depressive episodes; [d] Global Physical Illness Rating Scale of the Duke Older American Resources and Services Methodology; [e] Modified Hachinski Ischaemic Score; [f] Age at onset of depression; [g] Hamilton Depression Rating Scale; [h] Clinical Global Impression for Depression.

* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$.

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Findings illustrate the doubtful utility of qualitative evaluations of brain MR scans in informing depressive diagnosis in this age group. The present data differ from the (to our knowledge) other qualitatively-rated MRI study of elderly-only unipolar depressives that demonstrated significant and diffuse ventricular enlargement and cortical atrophy in patients as compared to age-matched normal controls (Rabins *et al*. 1991). Lack of consonance between studies may be accounted for by differences in samples and sample sizes, patient recruitment sites (in-patients *v*. mixed in-patients–out-patients), and MRI procedures and ratings. However, the inter-study differences may also simply reflect the marked heterogeneity of late-life depression (NIH Consensus Development Panel on Depression, 1992).

Within the depressed group, late-onset patients had more abnormal left medial temporal and left caudate ratings than current age-similar early-onset patients. The caudate finding is consistent with other neuroimaging investigations implicating the basal ganglia in mood disorders (Baxter *et al*. 1985; Buchsbaum *et al*. 1986; Mendez *et al*. 1989; Krishnan *et al*. 1992), including geriatric and late onset geriatric depression (Beats *et al*. 1991; Rabins *et al*. 1991; Coffey *et al*. 1989, 1990, 1993; Krishnan *et al*. 1992). In addition, the finding that caudate atrophy on the left, but not the right, significantly distinguished late-onset from early-onset groups is consistent with post-stroke depression studies that have reported an association between major depression and left sided basal ganglia infarcts (Starkstein *et al*. 1988). Neuroanatomical and neurochemical hypotheses regarding the possible role of basal ganglia pathology in the development of depression in the elderly have recently been described (Krishnan, 1993).

The temporal lobe has been related to emotional and neuroendocrine regulation, and has also been implicated in affective illness (Hauser *et al*. 1989; Krishnan, 1992; Sackheim *et al*. 1990), including geriatric depression (Bowen *et al*. 1989; Rabins *et al*. 1991; Wurthmann *et al*. 1992). Elevations of plasma and urinary-free cortisol concentrations have been reported in depressed patients (Carroll *et al*. 1976; Stokes *et al*. 1984) and pre-clinical studies suggest that glucocorticoid exposure results in hippocampal neuronal loss (Landfield *et al*. 1978; Sapolsky *et al*. 1985). Therefore, present findings could indicate that medial temporal atrophy might be a correlate or a consequence of late-onset major depression.

However, an alternative hypothesis is also suggested by our data. Medial temporal atrophy significantly correlated with the extended MMSE in the depressed group. Furthermore, global physical health ratings significantly correlated with all of the structural brain abnormalities measured except medial-temporal atrophy, suggesting that medial temporal changes are less likely to be related to extracerebral influences. In the context of a considerable literature identifying extensive pathological changes and neuroimaging evidence of atrophy in medial temporal lobe structures in Alzheimer's disease, including as an early marker (Hyman *et al*. 1984; Ball *et al*. 1985; Seab *et al*. 1988; deLeon *et al*. 1989, 1993; Kesslak *et al*. 1991; Jack *et al*. 1992; Jobst *et al*. 1992, 1994; Pearlson *et al*. 1992), these findings taken together are consistent with the notion that a subgroup of elderly depressives characterized by medial temporal lobe atrophy, older age and/or later age-at-onset, and cognitive disturbances might actually represent as-yet undeclared Alzheimer's disease (see Fig. 1) wherein depression is possibly an early pre-dementia expression (O'Brien *et al*. 1994). Other epidemiological (Devanand *et al*. 1996), clinical (Cole & Hickie, 1976; Burvill *et al*. 1989; Kral & Emery, 1989; Alexopoulos, 1990; Alexopoulos *et al*. 1993), genetic (Krishnan *et al*. 1994) and functional neuroimaging (Kumar *et al*. 1993) evidence support a possible relationship between late-life depression in some patients and Alzheimer's disease. Longitudinal follow-up of elderly depressed patients with and without medial temporal brain abnormalities will shed light on the possibility that these changes denote early Alzheimer's disease and are not merely a function of age-related atrophy.

Earlier investigators in late-life depression hypothesized that in a subgroup of elderly patients depression is mediated by underlying structural brain changes probably secondary to cerebrovascular disease (Kay, 1962; Post, 1962). This idea is supported by more recent findings demonstrating linkages between cerebrovascular disease risk factors and signal hyperintensities on intermediate and T2 weighted MR scans

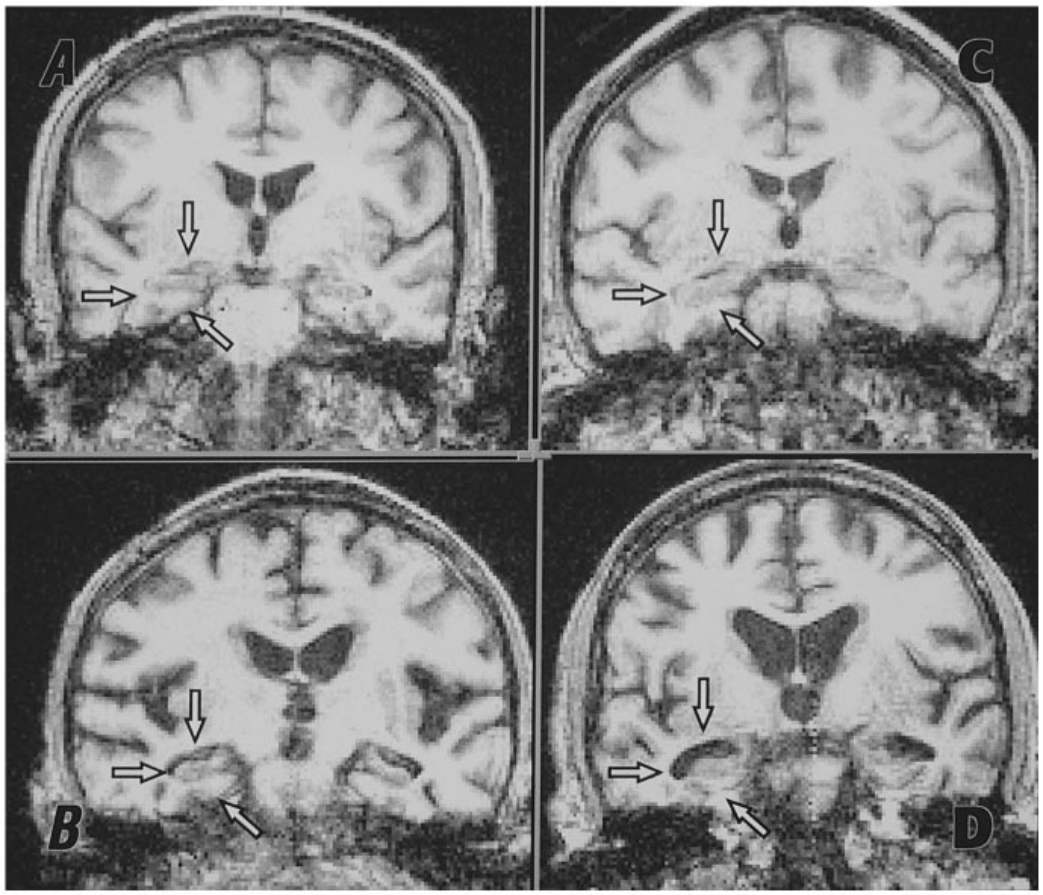

FIG. 1. Coronal magnetic resonance images of medial temporal lobe structures in elderly normal, depressed and Alzheimer's disease subjects. Coronal MR sections at the level of the mamillary bodies with arrows outlining normal medial temporal lobe anatomy in a 73-year-old normal control man (panel A) and a 70-year-old depressed man (panel C); and evidence for hippocampal and parahippocampal gyrus changes and temporal horn enlargement in an 83-year-old depressed man (panel B) and an 82-year-old Alzheimer's disease patient (panel D). Medial temporal structure changes in elderly depressives may identify early Alzheimer's disease.

(Awad *et al*. 1986; Sullivan *et al*. 1990), and associations between frequency/severity of such hyperintensities and geriatric, especially late-onset, depression (Coffey *et al*. 1988, 1990, 1993; Krishnan *et al*. 1988; Zubenko *et al*. 1990; Figiel *et al*. 1991; Lesser *et al*. 1991; Rabins *et al*. 1991; Fujikawa *et al*. 1993). In addition, the high incidence of depression following stroke (Robinson *et al*. 1984) further supports a relationship between cerebrovascular disease and affective disorder. However, in the present study of elderly depressives without a history of stroke or transient ischaemic attacks, MRI ratings of structural brain changes were not related to either the modified Hachinski rating or other measures of cerebrovascular disease risk, suggesting – at least in this population – a lesser role of vascular disease in atrophic brain changes. Taken together, the above reports and the current data support the view that within an umbrella category of later-onset geriatric depression, several subcategories probably exist with differing brain pathophysiological mechanism and contributions (e.g. vascular, neurodegenerative, mixed, metabolic).

Several other findings in this study are of interest. Global physical illness ratings were worse in patients than controls and correlated with MRI evidence of structural brain changes in the elderly depressed but not in normal

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comparison subjects. This supports that medical morbidity probably plays an important role in depression in the elderly (Alexopoulos, 1990; NIH Consensus Development Panel on Depression, 1992), and is consistent with both the notions that depression in late life may be mediated by an interaction between physical illness and structural brain changes and/or that a threshold level of physical illness may be necessary to contribute to atrophic brain abnormalities. In contrast to the global rating employed in this study, the use of physical illness rating scales that more sensitively assess specific organ/disease systems may generate hypotheses to explain how bodily and brain disease might relate. Somewhat surprisingly, age was not significantly associated with increasing brain atrophy, except for right medial temporal changes in the depressed group. Although age-related brain atrophy has been reported in neuroimaging studies of more mixed middle-aged, young-old, and old-old psychiatric populations (e.g. Zubenko *et al*. 1991; Krishnan *et al*. 1992), the lack of such a relationship in this study is most likely a consequence of the restricted age range of the subjects, wherein the majority fell between ages 70 and 80 years. Finally, third ventricle enlargement also significantly correlated with poorer performance on the extended MMSE in the depressed group. The third ventricle is formed by diencephalic structures (thalamus, hypothalamus), and its enlargement may reflect atrophic – and possibly functional – changes in thalamic association and relay nuclei (e.g. input from amygdala/hippocampus and output to prefrontal cortex) associated with cognitive/memory processes and emotion (Armstrong, 1990; Martin, 1996); and in hypothalamic nuclei implicated in neuroendocrine aspects of major depression (Stokes *et al*. 1984).

Ratings of general cortical atrophy might have obscured important findings in more anatomically delimited brain regions of interest (e.g. frontal lobe). Therefore, ongoing quantitative morphometry of MRI brain scans in this subject group may provide more sensitive measurements and also validate qualitative ratings. Sample sizes of early- and late-onset depressed elderly patients in this study were small, and conclusions must therefore be considered preliminary. Planned expansion and follow-up of the sample will allow further examination of relationships between structural brain changes and clinical features/outcomes and possibly facilitate the identification of neuroimaging-informed patient subgroups that may: (1) differentially respond to somatic antidepressant treatment; and (2) contribute to a more sophisticated nosology of late-life affective illness.

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APPENDIX 1
LATERAL VENTRICLES

0 Normal

1 Any two of the following:
- Moderate blunting of the lateral angles of the lateral ventricles at the central part and frontal horns.
- Moderate size of the lateral ventricles in at least two of three sections (frontal, body, occipital).
- Moderate asymmetry in size of the ventricle.
- Moderately abnormal shape of the lateral ventricle.

2 Extreme blunting of the lateral angles of the lateral ventricles at the central part or frontal horns, or;

Extreme size of the lateral ventricles in two of three sections (frontal, body, and occipital), or;

Any three of the following:
- moderate blunting of the lateral angles of the lateral ventricles at the central part and frontal horns;
- moderate size of the lateral ventricles in at least two of three sections (frontal, body, and occipital);
- marked asymmetry in size of the right and left lateral ventricles;
- markedly abnormal shape of the lateral ventricles.

3 Extreme blunting of the lateral angles of the lateral ventricles at the central part or frontal horns, and;

Extreme size of the lateral ventricles in two of three sections (frontal, body, and occipital).

THIRD VENTRICLE

0 Normal

1 Moderate widening of the third ventricle throughout its anterioposterior extent.

2 Marked widening of the third ventricle, particularly in the anterior portion.

3. Extreme widening of the third ventricle.

CORTEX

0 Normal

1 Diffuse and moderate enlargement of cortical sulci in the anterior, parietal, or occipital lobe, or;
Any two of the following:
moderate enlargement of the interhemispheric fissure;
moderate enlargement of the cortical subarachnoid space;
moderate enlargement of the subarachnoid cisterns.

2 Marked enlargement of the cortical sulci in the anterior, parietal, or occipital lobe, or;
Any two of the following:
marked enlargement of the interhemispheric fissure;
marked enlargement of the cortical subarachnoid space;
marked enlargement of the subarachnoid cisterns.

3 Marked enlargement of the cortical sulci in the anterior, parietal, or occipital lobe, and;
Any two of the following:
marked enlargement of the interhemispheric fissure;
marked enlargement of the cortical subarachnoid space;
marked enlargement of the subarachnoid cisterns.

MEDIAL TEMPORAL STRUCTURES

0 Normal

1 Any two of the following:
Moderate reduction in the size or abnormality of the shape of the hippocampus, amygdala, and parahippocampal gyrus;
Moderate enlargement of the temporal horn plus at least some abnormalities in the shape or size of the hippocampus, amygdala, and parahippocampal gyrus;
Moderate asymmetry of the shape or size of the hippocampus or temporal horn.

2 Marked reduction in the size or abnormality in the shape of the hippocampus, amygdala, and parahippocampal gyrus, or;
Marked enlargement of the temporal horn plus at least a moderate abnormality in the shape or size of the hippocampus, amygdala, and parahippocampal gyrus, or;
At least a moderate rating on both of the above two items.

3 Marked reduction in the size or abnormality in the shape of the hippocampus, amygdala, and parahippocampal gyrus, and;
marked enlargement of the temporal horn.

CAUDATE

0 Normal (at the level of the mamillary body, head of the caudate is a fully-developed half-circle shape extending into the ventricle).

1 Mild degree of flattening of the half-circle shape.

2 Moderate degree of flattening of the half-circle shape.

3 Entirely flattened.

REFERENCES

Alexopoulos, G. S. (1990). Clinical and biological findings in late-onset depression. In *American Psychiatric Press Review of Psychiatry*, *Vol 9* (ed. A. Tasman, S. M. Goldfinger and C. A. Kaufmann), pp. 249–262. American Psychiatric Press: Washington, DC.

Alexopoulos, G. S., Young, R. C. & Shindledecker, R. D. (1992). Brain computed tomography findings in geriatric depression and primary degenerative dementia. *Biological Psychiatry* **31**, 591–599.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Mattis, S. & Kakuma, T. (1993). The course of geriatric depression with 'reversible dementia': a controlled study. *American Journal of Psychiatry* **150**, 1693–1699.

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders* (*3rd edn. – Revised*) (*DSM-III-R*). American Psychiatric Association Press: Washington, DC.

Armstrong, E. (1990). Limbic thalamus: anterior and mediodorsal nuclei. In *The Human Nervous System* (ed. G. Paxinos), pp. 469–481. Academic Press: San Diego, Calif.

Awad, I. A., Spetzler, R. F., Hodak, J. A., Awad, C. & Carey, R. (1986). Incidental subcortical lesion identified on magnetic resonance imaging in the elderly: I. Correlation with age and cerebrovascular risk factor. *Stroke* **17**, 1084–1089.

Ball, M. J., Hachinski, V., Fox, A., Kirshen, A. J., Fisman, M., Blume, W., Kral, V. A., Fox, H. & Merskey, H. (1985). A new definition of Alzheimer's disease: a hippocampal dementia. *Lancet* i, 14–16.

Baxter, L. R., Phelps, M. E., Mazziotta, J. C., Schwartz, J. M., Gerner, R. H., Selin, C. E. & Sumida, R. M. (1985). Cerebral metabolic rates for glucose in mood disorders. Studies with PET and fluorodeoxyglucose F18. *Archives of General Psychiatry* **42**, 441–447.

Beats, B., Levy, R. & Forstl, H. (1991). Ventricular enlargement and caudate hyperdensity in elderly depressives. *Biological Psychiatry* **30**, 452–458.

Bowen, D. M., Najlerahim, A., Procter, A. W., Francis, P. T. & Murphy, E. (1989). Circumscribed changes of the cerebral cortex in neuropsychiatric disorders of later life. *Proceedings of the National Academy of Science* **86**, 9504–9508.

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Brown, F. W., Lewine, R. J., Hudgins, P. A. & Risch, S. C. (1992). White matter hyperintensity signals in psychiatric and non-psychiatric subjects. *American Journal of Psychiatry* **149**, 620–625.

Buchsbaum, M. S., Wu, J., DeLisi, L. E., Holcomb, H., Kessler, R., Johnson, J., King, A. C., Hazlett, A. E., Langston, K. & Post, R. M. (1986). Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with F2-deoxyglucose in affective illness. *Journal of Affective Disorders* **10**, 137–152.

Burvill, P. W., Hall, W. D., Stampfer, H. G. & Emmerson, J. P. (1989). A comparison of early onset and late onset depressive illness in the elderly. *British Journal of Psychiatry* **155**, 673–679.

Carroll, B. J., Curtis, G. C., Davies, B. M., Mendels, J. & Sugerman, A. A. (1976). Urinary-free cortisol excretion in depression. *Psychological Medicine* **6**, 43–50.

Coffey, C. E., Figiel, G. S., Djang, W. T., Cress, M., Saunders, W. B. & Weiner, R. D. (1988). Leukoencephalopathy in elderly depressed patients referred for ECT. *Biological Psychiatry* **24**, 143–161.

Coffey, C. E., Figiel, G. S., Djang, W. T., Saunders, W. B. & Weiner, R. D. (1989). White matter hyperintensity on magnetic resonance imaging: clinical and neuroanatomic correlates in the depressed elderly. *Journal of Neuropsychiatry* **1**, 135–144.

Coffey, C. E., Figiel, G. S., Djang, W. T. & Weiner, R. D. (1990). Subcortical hyperintensty on magnetic resonance imaging: a comparison of normal and depressed elderly subjects. *American Journal of Psychiatry* **147**, 187–189.

Coffey, C. E., Wilkinson, W. E., Weiner, R. D., Parashos, I. A., Djang, W. T., Webb, C. M., Figiel, G. S. & Spritzer, C. E. (1993). Quantitative cerebral anatomy in depression. A controlled magnetic resonance imaging study. *Archives of General Psychiatry* **50**, 7–16.

Cole, M. & Hickie, R. N. (1976). Frequency and significance of minor organic signs in elderly depressives. *Canadian Psychiatric Association Journal* **21**, 7–12.

deLeon, M. J., George, A. E., Stylopoulos, L. A., Smith, G. & Miller, D. C. (1989). Early marker for Alzheimer's disease: the atrophic hippocampus. *Lancet* ii, 672–673.

deLeon, M., Golomb, J., Golomb, J., George, A. E., Convit, A. J., Tarshish, C. Y., McRae, T., DeSanti, S., Smith, G., Ferris, S. H., Noz, M. & Rusinek, H. (1993). The radiologic prediction of Alzheimer disease: the atrophic hippocampal formation. *American Journal of Neuroradiology* **14**, 897–906.

Devanand, D. P., Sano, M., Tang, M. X., Taylor, S., Gurland, B. J., Wilder, D., Stern, Y. & Mayeux, R. (1996). Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Archives of General Psychiatry* **53**, 175–182.

Dolan, R. J., Calloway, S. P. & Mann, A. H. (1985). Cerebral ventricular size in depressed subjects. *Psychological Medicine* **15**, 873–878.

Duke University Center for the Study of Aging and Human Development. (1978). *Multidimensional Functional Assessment: The OARS Methodology*, *2nd edn*. Duke University Medical Center: Durham, NC.

Figiel, G. S., Krishnan, K. R. R., Doraiswamy, M. P., Rao, V. P., Nemeroff, C. B., Boyko, O. B. (1991). Subcortical hyperintensities on brain magnetic resonance imaging: a comparison between late age onset and early onset elderly depressed subjects. *Neurobiology of Aging* **26**, 245–247.

Folstein, M. F. & McHugh, P. R. (1978). Dementia syndrome of depression, in *Alzheimer's Disease: Senile Dementia and Related Disorders* (*Aging Vol. 7*) (ed. R. Katzman, R. D. Terry and K. L. Bick), pp. 87–93. Raven Press: New York.

Folstein, M. F., Folstein, S. E. & McHugh, P. R. (1975). 'Mini-Mental State': a practical method for grading cognitive state of patients for the clinician. *Journal of Psychiatric Research* **12**, 189–198.

Fujikawa, T., Yamawaki, S. & Touhouda, Y. (1993). Incidence of silent cerebral infarction in patients with major depression. *Stroke* **24**, 1631–1634.

Greenwald, B. S. & Kramer-Ginsberg, E. (1988). Age at onset of geriatric depression: relationship to clinical variables. *Journal of Affective Disorders* **15**, 61–68.

Guy, W. (ed.) (1976). *ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338*, pp. 534–537. Department of Health, Education, and Welfare: Washington, DC.

Hamilton, M. A. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* **23**, 56–62.

Hauser, P., Altshuler, L. L., Berrettini, W., Dauphinais, I. D., Gelernter, J. & Post, R. M. (1989). Temporal lobe measurement in primary affective disorder by magnetic resonance imaging. *Journal of Neuropsychiatry* **1**, 128–134.

Husain, M. M., McDonald, W. M., Doraiswamy, M., Figiel, G. S., Na, C., Escalona, R., Boyko, O. B., Nemeroff, C. B. & Krishnan, K. R. R. (1991). A magnetic resonance imaging study of putamen nuclei in major depression. *Psychiatry Research: Neuroimaging* **40**, 95–99.

Hyman, B. T., Van Hoesen, G. W., Damasio, A. R. & Barnes, C. L. (1984). Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. *Science* **225**, 1168–1170.

Jack, C. R., Peterson, R. C., O'Brien, P. C. & Tangalos, E. G. (1992). MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. *Neurology* **42**, 183–188.

Jacoby, R. J. & Levy, R. (1980). Computed tomography in the elderly: 3. Affective disorders. *British Journal of Psychiatry* **136**, 270–275.

Jacoby, R. J., Levy, R. & Bird, J. M. (1981). Computed tomography and the outcome of affective disorder: a follow-up study of elderly patients. *British Journal of Psychiatry* **139**, 288–292.

Jobst, K. A., Smith, A. D., Szatmari, M., Molyneux, A., Esiri, M. E., King, E., Smith, A., Jaskowski, A., McDonald, B. & Wald, N. (1992). Detection in life of confirmed Alzheimer's disease using a simple measurement of medial temporal lobe atrophy by computed tomography. *Lancet* **340**, 1179–1183.

Jobst, K. A., Smith, A. D., Szatmari, M., Esiri, M. M., Jaskowski, A., Hindley, N., McDonald, B. & Molyneux, A. J. (1994). Rapidly progressing atrophy of medial temporal lobe in Alzheimer's disease. *Lancet* **343**, 829–830.

Kay, D. W. K. (1962). Outcome and cause of death in mental disorders of old age: A long-term follow-up of functional and organic psychoses. *Acta Psychiatrica Scandanavica* **38**, 249–276.

Kesslak, J. P., Nalcioglu, O. & Cotman, C. W. (1991). Quantification of magnetic resonance scans for hippocampal and para-hippocampal atrophy in Alzheimer's disease. *Neurology* **41**, 51–54.

Kral, V. A. & Emery, O. B. (1989). Long term follow-up of depressive pseudodementia of the aged. *Canadian Journal of Psychiatry* **34**, 445–446.

Krishnan, K. R. R. (1992). Depression – neuroanatomical substrates. *Behavior Therapy* **23**, 571–583.

Krishnan, K. R. R. (1993). Neuroanatomic substrates of depression in the elderly. *Journal of Geriatric Psychiatry and Neurology* **1**, 39–58.

Krishnan, K. R. R., Goli, V., Ellinwood, E. H., France, R. D., Blazer, D. B. & Nemeroff, C. B. (1988). Leukoencephalopathy in patients diagnosed as major depressive. *Biological Psychiatry* **23**, 519–522.

Krishnan, K. R. R., McDonald, W. M., Escalona, P. R., Doraiswamy, P. M., Na, C., Husain, M. M., Figiel, G. S., Boyko, O. B., Ellinwood, E. H. & Nemeroff, C. B. (1992). Magnetic resonance imaging of the caudate nuclei in depression. Preliminary observations. *Archives of General Psychiatry* **49**, 553–557.

Krishnan, K. R. R., Ritchie, J. C., Tupler, L. A., McDonald, W. M., Knight, D., Nemeroff, C. B. & Marcovina, S. (1994). Apolipoprotein E e4. *Neurology* **44**, 2420–2421 (letter).

Kumar, A., Newberg, A., Alavi, A., Berlin, J., Smith, R. & Reivich, M. (1993). Regional cerebral glucose metabolism in late-life depression and Alzheimer's disease: a preliminary positron emission tomography study. *Proceedings of the National Academy of Science* **90**, 7019–7023.

Landfield, P., Waymire, J. & Lynch, G. (1978). Hippocampal aging and adrenocorticoids: a quantitative correlation. *Science* **202**, 1098–1102.

Lesser, I. M., Miller, B. L., Boone, K. B., Hill-Gutierrez, E., Mehringer, C. M., Wong, K. & Mena, I. (1991). Brain injury and

cognitive function in late-onset psychotic depression. *Journal of Neuropsychiatry and Clinical Neurosciences* **3**, 33–40.
Lieberman, J., Bogerts, B., Degreef, G., Ashtari, M., Lantos, G. & Alvir, J. (1992). Qualitative assessment of brain morphology in acute and chronic schizophrenia. *American Journal of Psychiatry* **149**, 784–794.
Martin, J. H. (1996). *Neuroanatomy: Text and Atlas*, *2nd edn*. Appleton & Lange: Stanford, Conn.
Mendez, M. F., Adams, N. L. & Lewandowski, K. S. (1989). Neurobehavioral changes associated with caudate lesions. *Neurology* **39**, 349–354.
Miller, D. S., Kumar, A., Yousem, D. M., Gottleib, G. L. (1994). MRI high-intensity signals in late-life depression and Alzheimer's disease. A comparison of subjects without major vascular risk factors. *American Journal of Geriatric Psychiatry* **2**, 332–337.
Murphy, E. (1983). Prognosis of depression in old age. *British Journal of Psychiatry* **142**, 111–119.
NIH Consensus Development Panel on Depression (1992). Diagnosis and treatment of depression in late life. *Journal of the American Medical Association* **268**, 1018–1024.
O'Brien, J. T., Desmond, P., Ames, D., Schweitzer, I., Tuckwell, V. & Tress, B. (1994). The differentiation of depression from dementia by temporal lobe magnetic resonance imaging. *Psychological Medicine* **24**, 633–640.
Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologica* **9**, 97–114.
Pearlson, G. D., Rabins, P. V., Kim, W. S., Speedie, L. J., Moberg, P. J., Burns, A. & Bascom, M. J. (1989). Structural brain CT changes and cognitive deficits in elderly depressives with and without reversible dementia ('pseudodementia'). *Psychological Medicine* **19**, 573–584.
Pearlson, G. D., Harris, G. J., Powers, R. E., Barta, P. E., Camargo, E. E., Chase, G. A., Noga, J. T. & Tune, L. E. (1992). Quantitative changes in mesial temporal volume, regional cerebral blood flow, and cognition in Alzheimer's disease. *Archives of General Psychiatry* **49**, 402–408.
Post, F. (1962). *The Significance of Affective Symptoms in Old Age. A Follow-up Study of One Hundred Patients*. Institute of Psychiatry, Maudsley Monographs No. 10, Oxford University Press: London.
Post, F. (1972). The management and nature of depressive illness in late life: a follow-through study. *British Journal of Psychiatry* **121**, 393–404.
Rabins, P. V., Pearlson, G. D., Aylward, E., Kumar, A. J. & Dowell, K. (1991). Cortical magnetic resonance imaging changes in elderly inpatients with major depression. *American Journal of Psychiatry* **148**, 617–620.
Robinson, R. G., Starr, L. B. & Price, T. R. (1984). A two year longitudinal study of post-stroke mood disorders: prevalence and duration at six months follow-up. *British Journal of Psychiatry* **144**, 256–262.
Rosen, W. G., Terry, R. D., Fuld, P. A., Katzman, R. & Peck, A. (1980). Pathological verification of ischemic score in differentiation of dementias. *Annals of Neurology* **7**, 486–488.
Rovner, B. W., German, P. S., Brant, L. J., Clark, R., Burton, L. & Folstein, M. F. (1991). Depression and mortality in nursing homes. *Journal of the American Medical Association* **265**, 993–996.
Sackheim, H. A., Prohovnik, I., Moeller, J. R., Brown, R. P., Apter, S., Prudic, J., Devanand, D. P. & Mukherjee, S. (1990). Regional cerebral blood flow in mood disorders. I. Comparison of major depressives and normal controls at rest. *Archives of General Psychiatry* **47**, 60–70.
Sapolsky, R., Krey, L. & McEwen, B. (1985). Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. *Journal of Neuroscience* **5**, 1221–1226.
Seab, J. P., Jagust, W. J., Wong, S. T. S., Roos, M. S., Reed, B. R. & Budinger, T. F. (1988). Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease. *Magnetic Resonance Medicine* **8**, 200–208.
Shima, S., Shikano, T., Kitamuna, T., Masuda, Y., Tsukomo, T., Kanba, S. & Asai, M. (1984). Depression and ventricular enlargement. *Acta Psychiatrica Scandanavica* **70**, 275–277.
Spitzer, R. L., Williams, J. B. W. & Bibbon, M. (1988). *Structured Clinical Interview for DSM-III-R*. Biometrics Research Department, NYS Psychiatric Institute: New York.
Starkstein, S., Robinson, R. G., Berthier, M. L., Parikh, R. M. & Price, T. R. (1988). Differential mood changes following basal ganglia vs thalamic lesions. *Archives of Neurology* **45**, 725–730.
Stokes, P. E., Stoll, P. M., Koslow, S. H., Maas, J. W., Swann, A. C. & Robins, E. (1984). Pretreatment DST and hypothalamic-pituitary-adrenocortical function in depressed patients and comparison groups. *Archives of General Psychiatry* **41**, 257–267.
Sullivan, P., Pary, R., Telang, F., Rifai, A. H. & Zubenko, G. S. (1990). Risk factors for white matter changes detected by magnetic resonance imaging in the elderly. *Stroke* **2**, 1424–1428.
Teng, E. L. & Chui, H. C. (1987). The modified Mini-mental state (3MS) examination. *Journal of Clinical Psychiatry* **48**, 314–318.
Wurthmann, C., Bogerts, B. & Hoft, B. (1992). Changes in brain morphology with senile depression: a morphometric study using computed tomography. *Deutsche Medizinische Wochenschrift* **117**, 443–447.
Zubenko, G. S., Sullivan, P., Nelson, J. P., Belle, S. H., Huff, F. J. & Wolf, G. L. (1990). Brain imaging abnormalities in mental disorders of late life. *Archives of Neurology* **47**, 1107–1111.