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Depression with late onset is associated with right frontal lobe atrophy

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ABSTRACT

Background. The objective of this study was to determine whether older adults with first-ever onset of depression after age 60 years (late onset depression, LOD) have smaller frontal lobes than elderly patients with early-onset depression (EOD) and aged controls.

Method. Twenty-seven subjects with LOD, 24 with EOD and 37 controls underwent volumetric MRI to determine right and left frontal lobe volumes and total brain volume.

Results. The right frontal volume of subjects with LOD was 8·0% and 5·6% smaller than that of patients with EOD ($P < 0{\cdot}01$) and controls (NS) respectively. Volume of the left frontal lobe was not significantly different from EOD or controls. All analyses were adjusted for age, gender and total brain volume. Unlike controls and those with EOD, patients with LOD did not display a significant positive correlation between cognitive scores and total brain, left frontal or right frontal volumes.

Conclusion. LOD is associated with right frontal lobe atrophy and loss of the correlation between cognitive performance and brain volume. This adds support to the fronto-striatal hypothesis of depression and suggests that structural brain changes have a particular role in cases of LOD.

INTRODUCTION

Depression is a common mental disorder in later life (Steffens *et al*. 2000) that has recently been associated with a number of brain abnormalities, as assessed by computed tomography and magnetic resonance imaging (MRI) (Soares & Mann, 1997). Cerebrovascular disease in the form of strokes (Burvill *et al*. 1995) or deep white matter disease (Nebes *et al*. 2001; O'Brien *et al*. 1996*a*) is frequent among older adults with depression, with some authors suggesting that late-onset depression (LOD) is the psychological expression of vascular brain pathology (Alexopoulos *et al*. 1997). However, brain abnormalities in later life depression are not limited to cerebrovascular disease. Coffey and colleagues (1993), in a detailed volumetric MRI analysis of the brains of 48 adults with severe depression, found that patients had significantly smaller frontal lobe volumes than 76 age and gender matched controls. Subsequent studies confirmed the presence of frontal lobe atrophy among patients with both major and minor depression in later life (Kumar *et al*. 1998) and suggested that the normal right-left frontal lobe asymmetry may be attenuated in older adults with a depressive disorder (Kumar *et al*. 2000*a*). However, it remains unclear whether these findings are limited to LOD or represent a feature of depression in later life regardless of age at onset. The present study was designed to clarify this question.

METHOD

Fifty-one older adults (in-patients, day-patients and out-patients) from two General Psychiatry Units and three geographically based Old Age

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Psychiatry services who met DSM-IV criteria for a major depressive episode were recruited. Thirty-seven age-matched controls were recruited mainly from spouses of these patients as well as others attending the same psychiatric services. All subjects provided written informed consent. LOD was defined as illness onset after age 60 years. All subjects had Mini-Mental State Examination (MMSE) scores of $\geqslant 24$ and a negative clinical history for strokes, transient ischaemic attacks, insulin-dependent diabetes or substance abuse and none had a formal contra-indication for MRI assessment. Clinical and demographic data were systematically collected from all subjects and included information on age, gender, handedness (as reported by the subject), years in full time education, smoking and alcohol history (past and present). Other assessment instruments included the DSM-IV checklist of symptoms (APA, 1994), Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979), National Adult Reading Test (NART) (Nelson & Willison, 1991), and the cognitive scale of the Cambridge Examination for Mental Disorders of the Elderly (CAMCOG) (Roth *et al*. 1988).

MRI scan procedure

All scans were performed on a 1.0 Tesla Siemens Magnetom Impact Expert MRI Scanner (Siemens Medical, Germany). T_1-weighted 3D MPRAGE (magnetization prepared rapid acquisition gradient echo) turbo flash sagittal sequence was used to acquire whole brain images (TR = 11·4 ms, TE = 4·4 ms, TI = 400 ms, TD = 50 ms, matrix 256 × 256, slice thickness = 1 mm). Standard head positioning was used and all images were acquired using the same plane (sagittal). De-identified imaging data was later transferred to a SUN Workstation for volumetric analysis with the Medical Information Display and Analysis System (MIDAS–3.0). All brain scans were analysed by O. P. A. according to the following steps: (1) segmentation of the whole 3D brain with the aim of excluding non-brain structures and tissues; (2) measurement of total brain volume; (3) blind load segmented brain image; (4) segmentation of the right frontal lobe using coronal view (assisted by a second window displaying the sagittal view of the brain), starting with the most anterior slice on which the corpus callosum could be seen and moving anteriorly to include all slices until no frontal lobe tissue is seen in the display window (over 30 slices); (5) measurement of frontal lobe volume; (6) repeat steps (4)–(5) for flipped image (always segmented on the right-hand side of the brain).

Reliability for total brain, right frontal and left frontal volume measurements was assessed by repeating measurements three times on five randomly selected scans. Mean coefficient of variation (standard deviation/mean) for total brain volume was 0·7% (range = 0·4 to 1·0%), 0·7% for the right frontal volume (range = 0·1 to 0·9%) and 0·5% for the left frontal volume (range = 0·1 to 0·8%).

Data analysis

Data were analysed with 'Stata7' (StataCorp, 2000). The frequency distribution of contingency tables was tested with Pearson's χ^2 or Fisher Exact Test (when the expected number of cases in two or more of four cells was <5). One-way analysis of variance was used to investigate between-group differences of normally distributed data (F statistic). Kruskal–Wallis χ^2 non-parametric analysis of variance was used to investigate between-group differences of numerical ordinal variables (e.g. years of education). Analysis of co-variance was used to adjust the statistical results for possible confounding variables, such as age, gender and total brain volume in the investigation of frontal lobe volume. Partial correlation coefficients were calculated to measure the strength of the association between CAMCOG scores and brain volumes while taking into account the age, pre-morbid intelligence (NART) score and MADRS scores of study participants. Partial correlations were also used to investigate the association between different measures of brain volume and age at onset of the depressive disorder. All tests were two-tailed.

RESULTS

Table 1 summarizes demographic and clinical information of elderly controls as well as subjects with EOD and LOD. Groups were well matched for age but there were more females in the EOD group. As expected, subjects with depression had significantly higher MADRS

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Table 1. *Demographic, clinical and brain volumetric characteristics of elderly controls and patients with early and late onset depressive disorder*

	Controls ($N=37$)	EOD ($N=24$)	LOD ($N=27$)	F, χ^2	P
Age (years)	72·9	72·8	75·5	1·54	NS
(95%CI)	(70·7–75·1)	(70·1–75·7)	(73·2–77·8)		
Gender female (%)	73·0	95·8	66·7	6·83	*
Education (years)	10·3	9·4	9·8	3·83	NS
(Range)	(6–16)	(4–16)	(7–17)		
Ever smoker (%)	59·5	45·8	59·3	1·30	NS
Current/never smoker (%)	16·7	18·7	31·2	1·19	NS
Alcohol consumption (weekly units)	2·3	1·8[a]	3·1	0·36	NS
(Range)	(0–24)	(0–10)	(0–20)		
Diabetes (%)	8·1	12·5	7·4	0·47	NS
Hypertension (%)	37·8	25·0	33·3	1·10	NS
Age at onset (mean score)	—	39·2	72·4	−12·42	***
(95%CI)[b]		(33·8–44·6)	(70·3–74·5)		
Lifetime number of weeks depressed (mean score)†	—	85·5	25·9	52·5	***
(95%CI)[b]		62–108	14·7–37		
Previous ECT treatment (%)[b]	—	41·7	18·5	3·28	NS
MADRS (mean score)	2·2	30·2	30·8	267	***
(95%CI)	(1·5–2·8)	(26·7–33·7)	(28·3–33·3)		
NART (mean IQ score)	110·4	104·2	104·1	3·37	*
(95%CI)	(106·7–114·1)	(100·0–108·4)	(99·2–109·0)		
CAMCOG (mean score)	96·8	90·0	87·5	2·31	NS[c]
(95%CI)	(95·1–98·5)	(86·9–98·1)	(84·2–90·0)		
Left handed (%)	5·4	0	14·8	4·59	NS
Total brain volume (mm^3)	1 062 517	1 053 932	1 052 080	0·02	NS[d]
(95%CI)	(1 033 742–1 091 293)	(1 016 474–1 091 391)	(1 017 318–1 086 841)		
Total frontal volume (mm^3)	97 339	99 036	93 291	3·32	*[e]
(95%CI)	(92 963–101 715)	(91 695–106 377)	(88 306–98 276)		
Right frontal volume (mm^3)	49 590	50 904	46 829	4·95	**[e]
(95%CI)	(47 386–51 793)	(47 298–54 510)	(44 009–49 649)		
Left frontal volume (mm^3)	47 749	48 131	46 461	1·45	NS[e]
(95%CI)	(45 483–50 014)	(44 171–52 092)	(44 091–48 832)		

EOD, Early-onset depression; LOD, late-onset depression; FET, Fisher's Exact Test.
† This information was only available for 16 and 18 patients with EOD and LOD respectively.
[a] Information was not available for one subject with early-onset depression.
[b] Only patients with early and late-onset depression were included in the analysis.
[c] After the analysis was controlled for age, NART and MADRS scores.
[d] After the analysis was controlled for gender and age.
[e] After the analysis was controlled for gender, age and total brain volume.
* $P<0·05$; ** $P<0·01$; *** $P<0·001$; NS, not significant.

scores than controls but there were no differences between EOD (mean MADRS 30·2) and LOD (mean MADRS 30·8). Elderly controls, EOD and LOD subjects had similar total brain volumes, although the frontal lobes of LOD patients were significantly smaller than the frontal lobes of EOD subjects (*post hoc* ANOVA, $F=5·62$, df $=1$, $P=0·022$, after the analysis was controlled for gender, total brain volume and age). Overall, LOD subjects had a total frontal lobe volume that was 5·8% and 4·2% smaller than that of subjects with EOD and controls respectively.

The right frontal lobes of study participants, as a group, were significantly larger than their respective left frontal lobes (paired $t=5·43$, $P<0·001$), although the expected difference between right and left frontal volumes was not observed among LOD subjects (paired $t=1·63$, $P=0·115$). The left frontal lobe volumes of elderly controls and patients with EOD and LOD were similar ($F=1·45$, df $=2$, $P=0·241$). Patients with LOD had smaller right frontal volumes than subjects with EOD (*post hoc* ANOVA, $F=9·18$, df $=1$, $P=0·004$); a similar trend was observed when they were compared to elderly controls (*post hoc* ANOVA, $F=3·29$, df $=1$, $P=0·075$). All analyses were adjusted for age, gender and total brain volume. The right frontal lobes of LOD patients were 5·6% and 8·0% smaller than the right frontal lobes of controls and EOD individuals.

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Table 2. *Partial correlations between CAMCOG scores and brain volumes (adjusted for age, NART and MADRS scores)*

	Controls ($N=37$)	EOD ($N=24$)	LOD ($N=27$)
Total brain volume	0·34*	0·48*	−0·24 NS
Left frontal volume	0·43**	0·63**	−0·18 NS
Right frontal volume	0·40*	0·61**	−0·20 NS

EOD, Early-onset depression; LOD, late-onset depression.
*$P<0·05$; ** $P<0·01$; NS, not significant.

We further investigated the association between left and right frontal lobe volumes with age at onset of the depressive disorder using partial correlation to adjust the analyses for the effects of age, total brain volume and gender. There was a trend for age at onset to be inversely correlated with right frontal ($r=-0·24$, $P=0·099$), but not left frontal volume ($r=-0·12$, $P=0·409$).

The partial correlation coefficients (adjusted for age, NART and MADRS scores) between cognitive scores (as measured by the CAMCOG) and total brain, left frontal and right frontal volumes for controls are summarized in Table 2. There was a significant positive correlation between cognitive performance (CAMCOG score) and brain volumes (including the frontal lobes) for elderly controls and older adults with EOD, but not for patients with LOD.

DISCUSSION

This study has demonstrated that LOD is associated with a relative reduction of frontal lobe volume of 5·8% compared to EOD and 4·2% reduction compared to controls. This is very similar to the findings of Coffey and colleagues (1993) who were the first to describe that patients with depression (mean age 62·4 years) had smaller frontal lobe volumes (7% in their study) than controls, although what proportion of their sample had LOD is not clear. Subsequent studies confirmed this finding among patients with illness onset after age 60 years (Kumar *et al.* 1998; Lai *et al.* 2000, but not Kumar *et al.* 1999) and are consistent with the results of functional imaging and neuropsychological investigations. For example, Lesser *et al.* (1994) found that depression was associated with decreased cerebral blood flow to the orbital frontal and inferior temporal lobes, and that blood flow to these brain regions was particularly low among the elderly. Similarly, Navarro *et al.* (2001) observed that older adults with onset of depression after age 50 years had significantly lower anterior frontal cerebral perfusion than age and gender matched controls (both right and left).

The results of the present study further indicate that patients with LOD have disproportionately smaller right frontal lobes than older adults with EOD or elderly controls. Previous reports had already described that patients with LOD disorders have smaller frontal volumes and display an attenuation of the right–left frontal lobe asymmetry (Dahabra *et al.* 1998; Kumar *et al.* 1998, 2000*b*), which we also observed. However, as well as supporting previous work, to our knowledge, this is the first study to show that this loss of both volume and asymmetry is limited to patients with LOD (i.e. it is not present among older adults with EOD).

There are understandable concerns that treating age at onset of depression as a dichotomous variable is methodologically problematical and that the forced division between 'early' and 'late' onset cases is somewhat arbitary and without much in the way of biological justification. We attempted to address this issue in three different ways: (1) the age cut-off adopted was chosen *a priori* before analysis based on the most frequent age cut-off in a number of similar studies (Baldwin & O'Brien, 2002); (2) we controlled our analyses of frontal lobe volumes for the effects of age, gender and total brain volume; (3) we investigated the association between left and right frontal lobe volumes with age at onset, using the latter as a continuous variable. The results of the partial correlation showed a trend approaching statistical significance supporting an inverse relationship between right frontal lobe volume and age at onset of the depressive disorder. This finding is compatible with the hypothesis that right frontal lobe pathology is more likely to be associated with depression with onset in later life.

The exact role of the frontal lobes in the pathogenesis of depression remains unclear, but there is substantial evidence from animal as well as from clinical and neuroimaging studies of

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humans that the frontal lobes modulate certain aspects of mood and cognitive functioning (Stuss & Benson, 1984; Fuster, 1996), and our study lends support to the hypothesis that disruption of fronto-subcortical circuitry is related to the development of depression. Several parallel fronto–striato–thalamo–cortical loops have been described by Alexander and colleagues and two, particularly involving dorsolateral prefrontal cortex and cingulate, have been implicated in mood regulation and the development of depression (Alexander *et al*. 1986, 1990). Subcortical white matter lesions in areas associated with these circuits, such as frontal lobe itself and basal ganglia, have been associated with depression in the elderly, especially LOD (O'Brien *et al*. 1996*a*; Greenwald *et al*. 1998), and the finding of volume loss would be compatible with the notion that dysfunction in such circuits is associated with the development of depression.

The origin of the reduced frontal lobe volume observed among patients with depression is unknown but, as our results indicate, they cannot be simply attributed to the ageing process. A 'deafferentation' atrophy resulting from a Wallerian degeneration due to the presence of the type of subcortical white matter changes described above remains a possibility. It is also possible that more subtle vascular changes might underpin the volume loss. While subjects with established cerebrovascular disease were carefully excluded from the current study, there is increasing evidence of a close relationship between vascular factors and depression and renewed interest that depression in late life may largely represent a 'vascular depression' (Alexopoulos *et al*. 1997; Krishnan *et al*. 1997; Baldwin & O'Brien, 2002), particularly in late onset cases. Using post-mortem material from depressed cases, we have previously shown an increase in atheromatous disease (Thomas *et al*. 2001) and molecular pathological changes localised in the frontal lobes (Thomas *et al*. 2000) that are consistent with the ischaemic damage despite the absence of macroscopic cerebrovascular disease. One possibility is that such ischaemic changes, which may be most common in LOD (Baldwin & O'Brien, 2002), might be causally related to the neuronal and glial changes which have been described in the frontal lobes of depressed subjects (Rajkowska *et al*. 1999), so producing measurable volume loss on structural MRI. Further clinico-pathological work, with imaging both *in vivo* and after death, will be needed to test this hypothesis and carefully examine radio-pathological correlations. It is unlikely that such volume loss is the result of potentially neurotoxic factors such as malnutrition, hypercortisolism (O'Brien *et al*. 1996*b*) or alcohol abuse. Patients with a history of alcohol abuse were excluded and, if damage were secondary to prolonged hypercortisolaemia, one would expect such changes to be more prominent among older adults with EOD, who had a significantly longer total history of depression, than LOD. However, it remains possible that the brains of LOD are, for some reason, more sensitive to the potentially toxic effects of such insults. Further work in this area should consider the possibility that there might be a modifying effect of subtype of depression (EOD *v*. LOD) as well as age.

The clinical significance of the loss of frontal lobe asymmetry amongst patients with depression is also unclear. The loss of certain brain asymmetries is often considered indicative of an abnormal development of brain lateralization in disorders such as schizophrenia (Kwon *et al*. 1999). If this loss of asymmetry has a neurodevelopmental origin, then it is possible that patients with LOD have a lifelong neurological predisposition to depression that becomes apparent as the number of stressors accumulate in later life (such as neuronal loss due to the ageing process, cerebrovascular disease, concomitant medical illness and grief). Interestingly, frontal lobe asymmetry has also been noted among children and adolescents with depression, but the asymmetry is somewhat different from that observed in old age. Nolan and colleagues (2002) reported that their young patients with a non-familial depressive disorder had significantly larger left but not right prefrontal cortical volumes than controls. One possible way of reconciling these results with our findings would be to speculate that the relative reduction of the right frontal lobe, either due to left frontal lobe enlargement or actual reduction in frontal lobe volume, is of aetiological significance for at least some cases of depression.

Another finding of the present study was that patients with LOD did not display the association between brain volume and cognitive

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performance observed in controls and older adults with EOD. Abas and colleagues (1990) have also noted this 'surprising' lack of correlation between cognitive performance and gross cortical atrophy scores measured with computed tomography among elderly patients with depression. In addition, the findings of recent studies indicate that performance across multiple cognitive domains is closely related to brain volume (Thompson *et al*. 2001). It is possible, therefore, that the lack of association between brain volume and cognitive performance results from the disproportionately higher loss of cells in the right frontal lobe of patients with LOD.

We have not as yet been able to determine the clinical significance of the neuroanatomical changes of LOD, and further work should clarify whether such changes have implications for the clinical presentation of patients and their response to treatment. In addition, there is a need to follow-up such subjects using serial scanning and accurate co-registration techniques (Fox *et al*. 1996) with the aim of clarifying whether the right frontal lobe atrophy of LOD is static (and more likely to be neurodevelopmental) or progressive (and more likely to be neurodegenerative).

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REFERENCES

Abas, M. A., Sahakian, B. J. & Levy, R. (1990). Neuropsychological deficits and CT scan changes in elderly depressives. *Psychological Medicine* **20**, 507–520.

Alexander, G. E., DeLong, M. R. & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience* **9**, 357–381.

Alexander, G. E., Crutcher, M. D. & DeLong, M. R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. *Progress in Brain Research* **85**, 119–146.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D. & Charlson, M. (1997). 'Vascular depression' hypothesis. *Archives of General Psychiatry* **54**, 915–922.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th edn*. American Psychiatric Association: Washington, DC.

Baldwin, R. C. & O'Brien, J. T. (2002). The vascular basis of late-onset depressive disorder. *British Journal of Psychiatry* **180**, 157–161.

Burvill, P. W., Johnson, G. A., Jamrozik, K. D., Anderson, C. S., Stewart-Wynne, E. G. & Chakera, T. M. (1995). Prevalence of depression after stroke: the Perth Community Stroke Study. *British Journal Psychiatry* **166**, 320–327.

Coffey, C. E., Wilkinson, W. E., Weiner, R. D., Parashos, I. A., Djang, W. T., Webb, M. C., 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.

Dahabra, S., Ashton, H. C., Bahrainian, M., Britton, P. G., Ferrier, I., McAllister, V. A., Marsh, V. R. & Moore, P. B. (1998). Structural and functional abnormalities in elderly patients clinically recovered from early and late-onset depression. *Biological Psychiatry* **44**, 34–46.

Fox, N. C., Freeborough, P. A. & Rossor, M. N. (1996). Visualisation and quantification of rates of atrophy in Alzheimer's disease. *Lancet* **348**, 94–97.

Fuster, J. M. (1996). Frontal lobe syndromes. In *Neuropsychiatry* (ed. B. S. Fogel, R. B. Schiffer and S. M. Rao), pp. 407–413. Williams & Wilkins: Baltimore.

Greenwald, B. S., Kramer-Ginsberg, E., Krishnan, K. R. R., Ashtari, M., Auerbach, C. & Patel, M. (1998). Neuroanatomic localization of magnetic resonance imaging signal hyperintensities in geriatric depression. *Stroke* **29**, 613–617.

Krishnan, K. R. R., Hays, J. C. & Blazer, D. C. (1997). MRI-defined vascular depression. *American Journal of Psychiatry* **154**, 497–501.

Kumar, A., Jin, Z., Bilker, W., Udupa, J. & Gottlieb, G. (1998). Late-onset minor and major depression: early evidence for common neuroanatomical substrates detected by using MRI. *Proceedings of the National Academy of Sciences USA* **95**, 7654–7658.

Kumar, A., Bilker, W., Lavretsky, H. & Gottlieb, G. (1999). Age of onset of depression and quantitative neuroanatomic measures: absence of specific correlates. *Psychiatry Research* **91**, 101–110.

Kumar, A., Bilker, W., Lavretsky, H. & Gottlieb, G. (2000*a*). Volumetric asymmetries in late-onset mood disorders: an attenuation of frontal asymmetry with depression severity. *Psychiatry Research* **100**, 41–47.

Kumar, A., Bilker, W., Jin, Z. & Udupa, J. (2000*b*). Atrophy and high intensity lesions: complementary neurobiological mechanisms in late-life major depression. *Neuropsychopharmacology* **22**, 264–274.

Kwon, J. S., McCarley, R. W., Hirayasu, Y., Anderson, J. E., Fisher, I. A., Kikinis, R., Jolesz, F. A. & Shenton, M. E. (1999). Left planum temporale volume reduction in schizophrenia. *Archives of General Psychiatry* **56**, 142–148.

Lai, T., Payne, M. E., Byrum, C. E., Steffens, D. C. & Krishnan, K. R. (2000). Reduction of orbital frontal cortex volume in geriatric depression. *Biological Psychiatry* **15**, 971–975.

Lesser, I. M., Mena, I., Boone, K. B., Miller, B. L., Mehringer, C. M. & Wohl, M. (1994). Reduction of cerebral blood flow in older depressed patients. *Archives of General Psychiatry* **51**, 677–686.

Lesser, I. M., Boone, K. B., Mehringer, C. M., Wohl, M. A., Miller, B. L. & Berman, N. G. (1996). Cognition and white matter hyperintensities in older depressed patients. *American Journal of Psychiatry* **153**, 1280–1287.

Montgomery, S. A. & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.

Navarro, V., Gasto, C., Lomena, F., Mateos, J. J. & Marcos, T. (2001). Frontal cerebral perfusion dysfunction in elderly late-onset major depression assessed by 99MTC-HMPAO SPECT. *Neuroimage* **14**, 202–205.

Nebes, R. D., Vora, I. J., Meltzer, C. C., Fukui, M. B., Williams, R. L., Kamboh, M. I., Saxton, J., Houck, P. R., DeKosky, S. T. & Reynolds, C. F. III (2001). Relationship of deep white matter hyperintensities and apolipoprotein E genotype to depressive symptoms in older adults without clinical depression. *American Journal of Psychiatry* **158**, 878–884.

Nelson, H. E. & Willison, J. (1991). *National Adult Reading Test (NART), 2nd edn*. NFER-Nelson: Windsor.

Nolan, C. L., Moore, G. J., Madden, R., Farchione, T., Bartoi, M., Lorch, E., Stewart, C. M. & Rosenberg, D. R. (2002). Prefrontal

https://doi.org/10.1017/S003329170300758X Published online by Cambridge University Press

cortical volume in childhood-onset major depression: preliminary findings. *Archives of General Psychiatry* **59**, 173–179.

O'Brien, J., Desmond, P., Ames, D., Schweitzer, I., Harrigan, S. & Tress, B. (1996*a*). A magnetic resonance imaging study of white matter lesions in depression and Alzheimer's disease. *British Journal of Psychiatry* **168**, 477–485.

O'Brien, J. T., Ames, D., Schweitzer, I., Colman, P., Desmond, P. & Tress, B. (1996*b*). Clinical and magnetic resonance imaging correlates of hypothalamic–pituitary–adrenal axis function in depression and Alzheimer's disease. *British Journal of Psychiatry* **168**, 679–687.

Rajkowska, G., Miguel-Hidalgo, J. J., Wei, J., Dilley, G., Pittman, S. D., Meltzer, H. Y., Overholser, J. C., Roth, B. L. & Stockmeier, C. A. (1999). Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biological Psychiatry* **45**, 1085–1098.

Roth, M., Huppert, F. A., Tym, E. & Mountjoy, C. Q. (1998). *CAMDEX-R: The Cambridge Examination for Mental Disorders of the Elderly-Revised*. Cambridge University Press: Cambridge.

Soares, J. C. & Mann, J. J. (1997). The anatomy of mood disorders – review of structural neuroimaging studies. *Biological Psychiatry* **41**, 86–106.

StataCorp (2000). *Stata Statistical Software: Release 7.0*. Stata Corporation: College Station, TX.

Steffens, D. C., Skoog, I., Norton, M. C., Hart, A. D., Tschanz, J. T., Plassman, B. L., Wyse, B. W., Welsh-Bohmer, K. A. & Breitner, J. C. (2000). Prevalence of depression and its treatment in an elderly population: the Cache County study. *Archives of General Psychiatry* **57**, 601–607.

Stuss, D. T. & Benson, D. F. (1984). Neuropsychological studies of the frontal lobes. *Psychological Bulletin* **95**, 3–28.

Thomas, A. J., Ferrier, I. N., Kalaria, R. N., Woodward, S. A., Ballard, C., Oakley, A., Perry, R. H. & O'Brien, J. T. (2000). Expression of ICAM-1 is increased in the dorsolateral prefrontal cortex in late-life depression. *American Journal of Psychiatry* **157**, 1682–1684.

Thomas, A. J., Ferrier, I. N., Kalaria, R. N., Perry, R. H., Brown, A. & O'Brien, J. T. (2001). A Neuropathological study of vascular factors in late-life depression. *Journal of Neurology, Neurosurgery and Psychiatry* **70**, 83–87.

Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V. P., Huttunen, M., Lonnqvist, J., Standertskjold-Nordenstam, C. G., Kaprio, J., Khaledy, M., Dail, R., Zoumalan, C. I. & Toga, A. W. (2001). Genetic influences on brain structure. *Nature Neuroscience* **4**, 1253–1258.

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