

Magnetic resonance imaging in late-life depression: vascular and glucocorticoid cascade hypotheses

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Background

Late-life depression is a common and heterogeneous illness, associated with structural abnormalities in both grey and white matter.

Aims

To examine the relationship between age at onset and magnetic resonance imaging (MRI) measures of grey and white matter to establish whether they support particular hypotheses regarding the anatomy and aetiology of network disruption in late-life depression.

Method

We studied 36 participants with late-life depression. Grey matter was examined using T_1 -weighted MRI and analysed using voxel-based morphometry. The hippocampus was automatically segmented and volume and shape analysis performed. White matter was examined using diffusion tensor imaging and analysed using tract-based spatial statistics.

Results

Later age at onset was significantly associated with reduced fractional anisotropy of widespread tracts, in particular the anterior thalamic radiation and superior longitudinal fasciculus. Earlier age at onset was associated with reduced hippocampal volume normalised to whole brain size bilaterally. However, no significant correlations were detected using hippocampal shape analysis or voxel-based morphometry.

Conclusions

Overall, the results were compatible with the vascular hypothesis, and provided some support for the glucocorticoid cascade hypothesis.

Declaration of interest

None.

Late-life depression is a multifactorial illness that is associated with neurobiological, psychological and social factors. With regard to the neurobiological factors, it is unlikely that depression is simply associated with abnormalities of a single brain region. Rather, it is postulated that depression is associated with disruption of the neural networks that regulate mood and behaviour. In particular, disruption of frontal-subcortical and limbic circuitry is hypothesised to play a key role in late-life depression.¹ Magnetic resonance imaging (MRI) studies have made an important contribution to the hypothesis that abnormalities in both grey and white matter contribute to network disruption in late-life depression. With regard to grey matter, a recent meta-analysis reported significant volume reductions in late-life depression in the hippocampus, orbito-frontal cortex, putamen and thalamus.² With regard to white matter, reduced integrity within frontal and temporal lobes has been frequently reported in late-life depression,³ as well as a more widespread pattern of white matter abnormalities.^{4,5} However, it is important to note that there is great heterogeneity in both grey and white matter findings to date. One possible explanation for the variation in the results of case-control studies is the range in age at onset within and between late-life depression groups studied. The nature and aetiology of such structural abnormalities in late-life depression is hypothesised to vary with age at onset. For this purpose, people with late-life depression are commonly divided into those with early- and those with late-onset depression, with various age cut-offs ranging from 50^{6,7} to 65⁸ employed.

The vascular depression hypothesis proposes that vascular factors (such as cardiovascular disease, diabetes, hypertension) may 'predispose, precipitate, or perpetuate' late-onset depression.⁹ Specifically, vascular factors are hypothesised to cause white

matter damage within frontal-subcortical circuits.^{1,9} In support of this hypothesis, late-onset depression is associated with more frequent and severe white matter hyperintensities compared with early-onset depression,¹⁰ and there is increasing evidence supporting a vascular basis for white matter hyperintensities in depression.^{11–14} However, few studies have examined the influence of age at onset on white matter integrity in late-life depression using diffusion tensor imaging (DTI). Bae *et al*¹⁵ compared fractional anisotropy between early-onset, late-onset depression and control groups. Although there were no significant differences in fractional anisotropy values between the early- and late-onset depression groups, the participants with early-onset depression displayed greater fractional anisotropy differences compared with control participants than did the participants with late-onset depression in several regions of interest.

Associations between age at onset and structural abnormalities will also be influenced by those with earlier age at onset, who have a longer duration of illness. The glucocorticoid cascade hypothesis was developed from animal models, in which stress-induced increases in glucocorticoid levels lead to regression of dendritic processes, inhibition of neurogenesis and neurotoxic effects in the hippocampus.¹⁶ Furthermore, as the hippocampus is a major site in the glucocorticoid negative feedback circuit on the hypothalamic-pituitary-adrenal (HPA) axis such effects will, in turn, result in further increases in glucocorticoid levels.¹⁷ In line with this theory, it follows that greater duration of illness will result in greater hippocampal damage because of repeated exposure to elevated glucocorticoid levels. Two studies of late-life depression have found negative associations between the duration of illness and hippocampal volume.^{18,19} However, several studies have failed to replicate this finding.^{20–23} Similarly, hippocampal volume has not been significantly associated with age at onset in

several studies of late-life depression,^{20,24,25} and has even been found to be negatively associated with age at onset in one.²²

It is important to note that the vascular and glucocorticoid hypotheses are neither mutually exclusive nor incompatible theories of late-life depression. Rather, the heterogeneity of depression indicates that multiple neural mechanisms may be implicated. For example, abnormalities in grey matter and white matter may also be related to Alzheimer's pathology.^{26,27} However, the relationship between onset of late-life depression and Alzheimer's disease is not yet clear, with both early- and late-onset depression associated with increased risk for dementia.²⁸ Therefore, in this paper, we focus on the relationship between age at onset and MRI measures in late-life depression with reference to the vascular and glucocorticoid cascade hypotheses. We expected that both the vascular and glucocorticoid hypotheses would have an impact on the results and hypothesised that (a) hippocampal volume would be positively associated with age at onset, in line with the glucocorticoid cascade hypothesis and (b) white matter integrity in frontal tracts would be negatively associated with age at onset, in line with the vascular hypothesis. We have separately reported comparison of this late-life depression group with a control group: white matter integrity was widely reduced in late-life depression, without significant group differences in grey matter measures.⁴

Method

Participants

The study was conducted with approval from the local research ethics committee (License 06/Q160/90). Informed written consent was obtained from all participants. Participants with late-life depression were identified from the general adult and old age psychiatric services of Oxford Health National Health Service Foundation Trust and also directly from the community by word of mouth and advertisements. Eligible participants were over the age of 60, with no potentially confounding comorbid medical, psychiatric or neurological conditions (including diagnoses of Alzheimer's disease or other dementias, bipolar disorder, mild cognitive impairment, Parkinson's disease, stroke, schizophrenia), and no implanted metallic devices, as required by standard MRI protocols. Participants with comorbid anxiety, controlled hypertension or diabetes were not excluded. Participants met the DSM-IV²⁹ criteria for major depression in the past, as assessed by an experienced psychiatrist, but were not necessarily currently depressed.

Clinical assessment

All participants underwent a clinical and neuropsychological assessment at the University of Oxford Centre for Clinical Magnetic Resonance Imaging (OCMR) or the University of Oxford Department of Psychiatry. A clinical assessment was performed by an experienced psychiatrist to verify inclusion and exclusion criteria, and determine age at onset, current symptom severity, current medication status, medical history and Framingham Stroke Risk.³⁰ Blood pressure and pulse were recorded for all participants and a more detailed physical examination was also performed if indicated by the history. Age at onset was defined as the age at which an individual experienced their first episode of major depression and was determined from personal testimony and hospital notes. Duration of illness was estimated by subtracting age at onset from current age. Current symptom severity was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD)³¹ and the 15-item Geriatric Depression Scale.³² Psychiatric medication was classified into the

following categories: anticonvulsant, antidepressant, anti-psychotic, anxiolytic and lithium salts. Framingham Stroke Risk was calculated based upon the following predictors: age, systolic blood pressure, diabetes mellitus, cigarette smoking, prior cardiovascular disease, atrial fibrillation, left ventricular hypertrophy (ascertained from personal testimony and hospital notes) and use of hypertensive medication. Electrocardiograms and glucose levels were not included as part of the clinical assessment.

A neuropsychological assessment was performed by trained graduate psychologists/neuroscientists and included the Addenbrooke's Cognitive Examination – Revised (ACE-R)³³ and the Mini-Mental State Examination (MMSE),³⁴ as measures of cognitive impairment. Tests included: Cambridge Neuropsychological Test Automated Battery (CANTAB) reaction time,³⁵ category fluency,³³ copied drawings,³³ clock drawing,³³ digit span,³⁶ digit symbol,³⁶ graded naming test,³⁷ Hopkins Verbal Learning Task – Revised (HVLT-R),³⁸ letter fluency,³³ Rey–Osterrieth complex figure (RCF)³⁹ and Trail Making Test (TMT) A and B.⁴⁰ Full results of the neuropsychological assessment performed are detailed elsewhere.⁴¹

Age at onset can either be treated as a continuous variable or divided into early- and late-onset depression. As division into early- and late-onset depression is not typically based upon reliable clinical or biological data, and as a result various age cut-offs have been used, we decided to treat age at onset as a continuous variable, as recommended by the MacArthur Foundation's workshop on late-life depression.⁴²

Statistical analysis was performed using PASW Statistics version 18 for Windows. Pearson's correlation was performed between age at onset and age, education, Framingham Stroke Risk, duration of illness, symptom severity and number of medications. An independent-samples *t*-test was performed to test whether age at onset differed between male and female participants.

MRI acquisition

All participants underwent an MRI scan at OCMR using a 3.0 Tesla Trio Siemens scanner with a 12-channel head-coil. High-resolution 3D T_1 -weighted MRI scans were acquired using a magnetisation-prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR) = 2040 ms, echo time (TE) = 4.7 ms, flip angle: 8, field of view (FOV) = 192 mm, voxel dimension: 1 mm isotropic). Whole-brain DTI was acquired using an echoplanar imaging (EPI) sequence (TR = 7900/7800 ms, TE = 98/82 ms, FOV = 240 mm, voxel size: 2.5 mm isotropic, *b* value: 1000, number of directions: 60, number of acquisitions: 2).

MRI analysis

Image analysis was performed using tools from the FMRIB (Functional MRI of the Brain) software library (FSL version 4.1, www.fmrib.ox.ac.uk/fsl/) on a UNIX-based GNU/Linux operating system.⁴³

Whole brain volume

T_1 -weighted images were brain-extracted using the brain extraction tool (BET version 2.1).⁴⁴ Whole brain volumes were calculated and correlated with age at onset using partial correlation analysis, with age and gender as covariates.

Hippocampal volume and shape

Segmentation and vertex analysis of the hippocampus was performed using an automated model-based segmentation tool (FMRIB's integrated registration and segmentation tool, FIRST

version 1.2).⁴⁵ First, T_1 -weighted images were aligned to Montreal Neurological Institute (MNI) 152 space at 1 mm resolution using three-stage affine registration. Second, based on the learned models of manually labelled images, linear combinations of shape modes of variation were searched through for the most probable shape instance given the observed intensities in the T_1 -weighted image. Third, boundary correction classified boundary voxels in the volumetric output. Both the registrations and subsequent segmentations were manually checked for errors and none was found.

Hippocampal volume was extracted and expressed as a percentage of whole brain volume. Normalised hippocampal volume was correlated with age at onset using partial correlation analysis with age and gender as covariates.

Vertex-wise statistics examining hippocampal shape were performed in MNI space using FIRST, with age and gender included as confound regressors. This tool, FIRST, employs a multivariate general linear model to test for correlations between age at onset and mean vertex location, using Pillai's trace to derive F -statistic values. False discovery rate correction for multiple comparisons was then applied to obtain thresholded F statistics.

Voxel-based morphometry

Voxel-based morphometry analysis was performed using FSL-VBM version 1.1.^{46,47} Grey matter partial volume images were aligned to MNI 152 standard space using the affine registration tool FMRIB's linear image registration tool (FLIRT version 5.5),^{48,49} followed by non-linear registration using FMRIB's non-linear image registration tool (FNIRT version 1.0),^{50,51} which uses a b-spline representation of the registration warp field.⁵² The resulting images were averaged to create a study-specific template, to which the native grey matter images were then non-linearly re-registered. The registered partial volume images were then modulated by dividing by the Jacobian of the warp field. The modulated segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Voxel-wise statistics were performed using Randomise version 2.1, a permutation-based inference tool for non-parametric statistical thresholding that corrects for multiple comparisons across space.⁵³ The significance threshold for correlations with age at onset was set at $P < 0.05$, using the threshold-free cluster enhancement (TFCE) option, with age and gender included as confound regressors.⁵⁴ As modulation in FSL-VBM is based only on the non-linear registration stage, rather than both the affine and non-linear stages of registration, it was

not necessary to also include whole brain volume as a confound regressor.

White matter integrity

The DTI data were manually checked and artefacts removed before eddy-current correction was run to correct for eddy-current induced distortions and head motion.

Tract-based spatial statistics

Analysis of the DTI data was carried out using Tract-Based Spatial Statistics (TBSS version 1.2).⁵⁵ Fractional anisotropy images were created by fitting a tensor model to the raw diffusion data using FMRIB's diffusion toolbox, and then brain-extracted using BET.⁴⁴ All participants' fractional anisotropy data were then aligned into a common space using FNIRT.^{50,51} Next, the mean fractional anisotropy image was created and thinned to create a mean fractional anisotropy skeleton that represents the centres of all tracts common to the group. Each participant's aligned fractional anisotropy data were then projected onto this skeleton. Voxel-wise statistics were performed using Randomise,⁵³ with age and gender included as confound regressors. The significance threshold for correlations with age at onset was set at $P < 0.05$, using the TFCE option.⁵⁴

To aid in the localisation of significant differences in fractional anisotropy, skeleton masks (tracts of interest, TOI) were created for the anterior thalamic radiation; genu, body, and splenium of the corpus callosum; cingulum; corticospinal tract; fornix; inferior longitudinal fasciculus; superior longitudinal fasciculus; and uncinate fasciculus. The TOI were based on the International Consortium for Brain Mapping ICBM-DTI-81 White-Matter Labels Atlas and the JHU (Johns Hopkins University) White-Matter Tractography Atlas within the FSL atlas tool, as well as the MRI Atlas of Human White Matter.⁵⁶ The percentage of mask voxels that were significantly different in fractional anisotropy was calculated for each TOI.

Results

Demographic data are presented in Table 1. Age at onset ranged from 10 to 78 years; distribution of age at onset is illustrated in online Fig. DS1. Age at onset did not differ between males and females ($t_{34} = 1.404$, $P = 0.169$) and was not correlated with age,

Table 1 Demographic data

	Late-life depression	r	P
Participants, n	36	N/A	N/A
Gender, female:male, n	24:12	N/A	N/A
Age at onset, mean (s.d.)	45.39 (18.97)	N/A	N/A
Age, mean (s.d.)	71.83 (7.71)	0.238	0.163
Cognitive impairment			
Addenbrooke's Cognitive Examination – Revised	91.50 (6.26)	–0.369	0.027
Mini-Mental State Examination	28.97 (1.36)	–0.348	0.038
Years of education, mean (s.d.)	13.94 (3.74)	–0.279	0.099
Framingham Stroke Risk, mean (s.d.)	10.64 (4.11)	0.056	0.745
Duration of illness, mean (s.d.)	26.44 (18.70)	–0.916	<0.001
Severity			
Hamilton Rating Scale for Depression	4.19 (4.77)	0.067	0.699
Geriatric Depression Scale	3.83 (3.47)	–0.119	0.496
Number of current medications, mean (s.d.)	1.44 (0.77)	0.099	0.566
N/A, not applicable.			
a. Data shown in bold indicate correlation with age at onset is statistically significant ($P < 0.05$).			

gender, education, Framingham Stroke Risk or number of medications (Table 1). Age at onset was strongly associated with duration of illness and moderately associated with cognitive impairment (Table 1).

The HRSD scores ranged from 0 to 18. Twenty-seven participants had HRSD scores indicative of remission ($\text{HRSD} \leq 7$). In total 33 participants were currently taking antidepressants, 7 anti-psychotics, 5 anxiolytics, 4 lithium salts and 1 an anticonvulsant. Two participants were not currently receiving any psychotropic medication. Participants received the following medication for other medical complaints: analgesics (pizotifen, carbamazepine, paracetamol; three participants); antacids and proton pump inhibitors (three participants); anti-arthritis drugs (glucosamine sulphate; one participant); anticancer adjuvant drugs (anastrozole, Iscador; two participants); anti-diarrheal drugs (one participant); antihypertensives (four participants angiotensin-converting-enzyme (ACE) inhibitors, three participants angiotensin II receptor antagonists, one participant beta-blockers, four participants calcium-channel blockers, five participants diuretics); aspirin (two participants); calcium (two participants); cholesterol lowering drugs (ciprofibrate, statins; eight participants); hypnotics (two participants); inhalers (salbutamol; three participants); non-steroidal anti-inflammatories (NSAIDs; two participants); oral antidiabetics (four participants); steroids (two participants); and thyroxine (one participant).

Grey matter

There was a moderate negative correlation between age at onset and whole brain volume ($r = -0.372$, $P = 0.03$; online Fig. DS2), and a moderate-to-strong positive correlation with normalised hippocampal volume on both sides (left: $r = 0.504$, $P = 0.002$; right: $r = 0.411$, $P = 0.016$; online Fig. DS3). There were no significant correlations between age at onset and hippocampal shape. Also, no significant correlations between age at onset and grey matter were detected using FSL-VBM.

White matter

There were widespread negative correlations between age at onset and fractional anisotropy, with 20% of skeleton voxels significant at $P < 0.05$. The spatial distribution of significant negative correlations is summarised in Fig. 1 and Table 2 (see online Fig. DS4 for a colour version of Fig.1). The anterior thalamic radiation and superior longitudinal fasciculus were particularly affected, with 63% and 54% of voxels significant respectively (Table 2, online Fig. DS5). There were no regions where age at onset was positively correlated with fractional anisotropy.

Discussion

In this paper, we investigated the relationships between age at onset and MRI measures of grey and white matter. Age at onset was negatively correlated with fractional anisotropy in widespread regions. In particular, later age at onset was associated with reduced fractional anisotropy within the anterior thalamic radiation and superior longitudinal fasciculus, both of which project to the frontal lobe. This result is in line with a greater prevalence and severity of white matter hyperintensities in late-compared with early-onset depression,¹⁰ and is compatible with the vascular depression hypothesis, which proposes that a later age at onset is associated with a greater degree of white matter abnormalities in frontal-subcortical and limbic tracts.⁹ A positive correlation between age at onset and Framingham Stroke Risk Score would have added further support to the vascular depression hypothesis, but was not detected. However, it has been

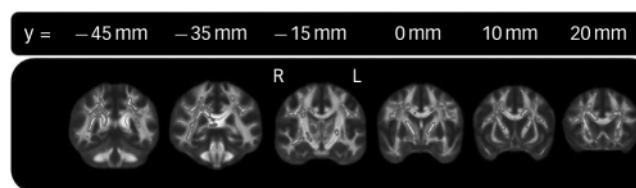


Fig. 1 Localisation of correlations between fractional anisotropy and age at onset.

Regions significantly correlated ($P < 0.05$) between age at onset and fractional anisotropy in late-life depression are shown dilated for illustrative purposes and overlaid on a thinner skeleton. Age and gender were included as confound regressors. See online Fig. DS1 for a colour version of this figure.

proposed that stroke risk factors may not be predictive of more subtle cerebrovascular disease.⁵⁷ For example, stroke risk scores do not include total cholesterol and high-density lipoprotein cholesterol as predictors, both of which can contribute to risk of cerebrovascular disease. In order to assess the vascular depression hypothesis more directly, future studies should include markers of vascular disease, for example measures of carotid intima-media thickness, pulse wave velocity, pulse wave analysis, orthostatic hypotension, heart rate variability or baroreflex sensitivity.^{11,12,58–60}

Earlier age at onset was associated with reduced normalised bilateral hippocampal volumes. As duration of illness was calculated by subtracting age at onset from current age, and all analyses included age as a covariate, this finding is in line with studies that found greater duration of illness to be associated with reduced hippocampal volume.^{18,19} Furthermore, this result is compatible with the glucocorticoid cascade hypothesis, which proposes that hippocampal damage results from repeated exposure to elevated cortisol levels.¹⁶ However, a study directly examining the relationship between hippocampal volume and cortisol levels in late-life depression found that hippocampal volume reduction was not associated with increased cortisol levels.²² Similarly, Gerritsen *et al*⁶¹ found that although early-onset depression was associated with reduced hippocampal volumes compared with control participants, it was not associated with alterations in basal HPA axis regulation. Also, in contrast to the pattern of selective volume loss in the dentate gyrus and CA3 subfields, which is associated with stress-related damage in animal studies⁶² and post-traumatic stress disorder,⁶³ there was an absence of localised hippocampal changes in late-life depression. An alternative explanation offered is that reduced hippocampal volume in early-onset depression pre-dates and predisposes to

Table 2 Localisation of correlations between fractional anisotropy and age at onset

Tract of interest	% ^a
Whole skeleton	20
Anterior thalamic radiation	63
Corticospinal tract	8
Cingulum	6
Corpus callosum	
Body	17
Genu	25
Splenium	21
Fornix	12
Inferior longitudinal fasciculus	10
Superior longitudinal fasciculus	54
Uncinate fasciculus	6

a. Percentage of voxels displaying a significant correlation between fractional anisotropy and age ($P < 0.05$) in each tract of interest.

depression onset. In support of this explanation, reduced hippocampal volume has been detected in 'at risk' groups.^{64,65} Longitudinal studies examining hippocampal volume are needed, as 'at risk' groups may also include participants who are resilient to developing depression.

Methodological considerations

As with the majority of MRI studies of late-life depression, sample size is the main limitation of this study. A key strength was the wide range of age at onset within the late-life depression group, which spanned from 10 to 78 years of age. However, although patient testimony was combined with use of hospital notes, estimation of age at onset may have been susceptible to recall bias where hospital notes were limited.^{66,67} The definition of age at onset as the age at which an individual experiences their first episode of major depression did not take into account prior episodes of subsyndromal depression, which may have resulted from the same pathophysiology as later episodes of major depression. However, consistent and accurate identification of the onset of subsyndromal depression is arguably more difficult to obtain compared with the onset of major depression.⁴² The possibility of recall bias also contributed to our decision to calculate illness duration by subtracting age at onset from current age. Calculation of the total number of days depressed using the total number of episodes and the length of each episode may represent a more accurate marker of illness duration, but is extremely difficult to accurately assess in a retrospective study of late-life depression. Calculation of Framingham Risk Score was limited by electrocardiograms not being performed and diabetes not being tested for at the time of the assessment.

We have previously reported differences in grey and white matter between the participants with late-life depression reported in this paper and an age-matched control group.⁴ Whereas late-life depression was associated with widespread reductions in white matter integrity, hippocampal volume was not significantly different between groups. Our finding that earlier age at onset is associated with reduced hippocampal volume within late-life depression in this paper offers a possible explanation as to why our sample of participants with late-life depression, when considered as a whole, did not differ from a control group, in contrast to some of the literature.^{2,68}

Implications

Overall, older age at onset was associated with reduced fractional anisotropy in frontal tracts, supportive of the vascular hypothesis. Younger age at onset was associated with greater duration of illness and reduced hippocampal volume within late-life depression, compatible with the glucocorticoid cascade hypothesis. Future studies should use direct markers in order to explore these hypotheses in greater depth.

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References

- Alexopoulos GS. Frontostriatal and limbic dysfunction in late-life depression. *Am J Geriatr Psychiatry* 2002; **10**: 687–95.
- Sexton CE, Mackay CE, Ebmeier KP. A systematic review and meta-analysis of magnetic resonance imaging studies in late-life depression. *Am J Geriatr Psychiatry* 2012; Feb 29 (Epub ahead of print).
- Sexton CE, Mackay CE, Ebmeier KP. A systematic review of diffusion tensor imaging studies in affective disorders. *Biol Psychiatry* 2009; **66**: 814–23.
- Sexton CE, Allan CL, Le Masurier M, McDermott LM, Kalu UG, Herrmann LL, et al. Magnetic resonance imaging in late-life depression: multi-modal examination of network disruption. *Arch Gen Psychiatry* 2012; in press.
- Shimony JS, Sheline YI, D'Angelo G, Epstein AA, Benzinger TL, Mintun MA, et al. Diffuse microstructural abnormalities of normal-appearing white matter in late life depression: a diffusion tensor imaging study. *Biol Psychiatry* 2009; **66**: 245–52.
- Pantel J, Schroder J, Essig M, Popp D, Dech H, Knopp MV, et al. Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. *J Affect Disord* 1997; **42**: 69–83.
- Taylor WD, Steffens DC, Payne ME, MacFall JR, Marchuk DA, Svenson IK, et al. Influence of serotonin transporter promoter region polymorphisms on hippocampal volumes in late-life depression. *Arch Gen Psychiatry* 2005; **62**: 537–44.
- Avila R, Ribeiz S, Duran FL, Arrais JP, Moscoso MA, Bezerra DM, et al. Effect of temporal lobe structure volume on memory in elderly depressed patients. *Neurobiol Aging* 2009; **32**: 1857–67.
- Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry* 1997; **54**: 915–22.
- Herrmann L, Lemasurier M, Ebmeier K. White matter hyperintensities in late life depression: a systematic review. *J Neurol Neurosurg Psychiatry* 2008; **79**: 619–24.
- Chen CS, Chen CC, Kuo YT, Chiang IC, Ko CH, Lin HF. Carotid intima-media thickness in late-onset major depressive disorder. *Int J Geriatr Psychiatry* 2006; **21**: 36–42.
- Smith PJ, Blumenthal JA, Babyak MA, Doraiswamy PM, Hinderliter A, Hoffman BM, et al. Intima-media thickness and age of first depressive episode. *Biol Psychol* 2009; **80**: 361–4.
- Thomas AJ, O'Brien JT, Davis S, Ballard C, Barber R, Kalaria RN, et al. Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study. *Arch Gen Psychiatry* 2002; **59**: 785–92.
- Thomas AJ, Perry R, Kalaria RN, Oakley A, McMeekin W, O'Brien JT. Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. *Int J Geriatr Psychiatry* 2003; **18**: 7–13.
- Bae JN, MacFall JR, Krishnan KR, Payne ME, Steffens DC, Taylor WD. Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. *Biol Psychiatry* 2006; **60**: 1356–63.
- Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 2000; **57**: 925–35.
- Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocr Rev* 1986; **7**: 284–301.
- Bell-McGinty S, Butters MA, Meltzer CC, Greer PJ, Reynolds 3rd CF, Becker JT. Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. *Am J Psychiatry* 2002; **159**: 1424–7.
- Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 1996; **93**: 3908–13.
- Andresescu C, Butters MA, Begley A, Rajji T, Wu M, Meltzer CC, et al. Gray matter changes in late life depression – a structural MRI analysis. *Neuropsychopharmacology* 2008; **33**: 2566–72.

- 21 Janssen J, Hulshoff Pol HE, de Leeuw FE, Schnack HG, Lampe IK, Kok RM, et al. Hippocampal volume and subcortical white matter lesions in late life depression: comparison of early and late onset depression. *J Neuro Neurosurg Psychiatry* 2007; **78**: 638–40.
- 22 O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N. A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *Am J Psychiatry* 2004; **161**: 2081–90.
- 23 Weber K, Giannakopoulos P, Delaloye C, de Bilbao F, Moy G, Moussa A, et al. Volumetric MRI changes, cognition and personality traits in old age depression. *J Affect Disord* 2010; **124**: 275–82.
- 24 Ashtari M, Greenwald BS, Kramer-Ginsberg E, Hu J, Wu H, Patel M, et al. Hippocampal/amygdala volumes in geriatric depression. *Psychol Med* 1999; **29**: 629–38.
- 25 Steffens DC, Byrum CE, McQuoid DR, Greenberg DL, Payne ME, Blitchington TF, et al. Hippocampal volume in geriatric depression. *Biol Psychiatry* 2000; **48**: 301–9.
- 26 Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds 3rd CF, et al. Pathways linking late-life depression to persistent cognitive impairment and dementia. *Dialogues Clin Neurosci* 2008; **10**: 345–57.
- 27 Caraci F, Copani A, Nicoletti F, Drago F. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. *Eur J Pharmacol* 2010; **626**: 64–71.
- 28 Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol* 2011; **7**: 323–31.
- 29 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th edn) (DSM-IV)*. APA, 1994.
- 30 D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke* 1994; **25**: 40–3.
- 31 Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967; **6**: 278–96.
- 32 Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982; **17**: 37–49.
- 33 Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* 2006; **21**: 1078–85.
- 34 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–98.
- 35 Sahakian BJ, Owen AM, Morant NJ, Eagger SA, Boddington S, Crayton L, et al. Further analysis of the cognitive effects of tetrahydroaminoacridine (THA) in Alzheimer's disease: assessment of attentional and mnemonic function using CANTAB. *Psychopharmacology (Berl)* 1993; **110**: 395–401.
- 36 Wechsler D. *Wechsler Adult Intelligence Scale*. The Psychological Corporation, 1997.
- 37 McKenna P, Warrington EK. Testing for nominal dysphasia. *J Neuro Neurosurg Psychiatry* 1980; **43**: 781–8.
- 38 Brandt J. The Hopkins verbal learning test: development of a new memory test with six equivalent forms. *Clin Neuropsychol* 1991; **5**: 125–42.
- 39 Osterrieth PA. Le test de copie d'une figure complexe. *Arch Psychol* 1944; **30**: 206–356.
- 40 Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* 1958; **8**: 271–6.
- 41 Sexton CE, McDermott L, Kalu UG, Herrmann LL, Bradley KM, Allan CL, et al. Exploring the pattern and neural correlates of neuropsychological impairment in late-life depression. *Psychol Med* 2011; Oct 26 (Epub ahead of print).
- 42 Lyness JM, Pearson JL, Lebowitz BD, Kupfer DJ. Age at onset or late-life depression: a research agenda report of a MacArthur Foundation-NIMH Workshop. *Am J Geriatr Psychiatry* 1994; **2**: 4–8.
- 43 Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004; **23** (suppl 1): S208–19.
- 44 Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002; **17**: 143–55.
- 45 Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage* 2011; **56**: 907–22.
- 46 Ashburner J, Friston KJ. Voxel-based morphometry – the methods. *Neuroimage* 2000; **11**: 805–21.
- 47 Good CD, Johnsrude IS, Ashburner J, Henson RNA, Friston KJ, Frackowiak RSJ. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001; **14**: 21–36.
- 48 Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 2002; **17**: 825–41.
- 49 Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal* 2001; **5**: 143–56.
- 50 Andersson JLR, Jenkinson M, Smith S. *Non-Linear Optimisation*. *FMRIB Technical Report TR07JA1*. FMRIB, 2007 (www.fmrib.ox.ac.uk/analysis/techrep/).
- 51 Andersson JLR, Jenkinson M, Smith S. *Non-Linear Registration, aka Spatial Normalisation*. *FMRIB Technical Report TR07JA2*. FMRIB, 2007 (www.fmrib.ox.ac.uk/analysis/techrep/).
- 52 Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging* 1999; **18**: 712–21.
- 53 Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* 2002; **15**: 1–25.
- 54 Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* 2009; **44**: 83–98.
- 55 Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006; **31**: 1487–505.
- 56 Mori S, Wakana S, Nagae-Poetscher LM, van Zijl PCM. *MRI Atlas of Human White Matter*. Elsevier BV, 2005.
- 57 Thomas AJ, Kalara RN, O'Brien JT. Depression and vascular disease: what is the relationship? *J Affect Disord* 2004; **79**: 81–95.
- 58 Paranthaman R, Greenstein AS, Burns AS, Cruickshank JK, Heagerty AM, Jackson A, et al. Vascular function in older adults with depressive disorder. *Biol Psychiatry* 2010; **68**: 133–9.
- 59 Richardson J, Kerr SR, Shaw F, Kenny RA, O'Brien JT, Thomas AJ. A study of orthostatic hypotension in late-life depression. *Am J Geriatr Psychiatry* 2009; **17**: 996–9.
- 60 Vasudev A, O'Brien JT, Tan MP, Parry SW, Thomas AJ. A study of orthostatic hypotension, heart rate variability and baroreflex sensitivity in late-life depression. *J Affect Disord* 2011; **131**: 374–8.
- 61 Gerritsen L, Comijs HC, van der Graaf Y, Knops AJ, Penninx BW, Geerlings MI. Depression, hypothalamic pituitary adrenal axis, and hippocampal and entorhinal cortex volumes – the SMART medea study. *Biol Psychiatry* 2011; **70**: 373–80.
- 62 McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. *Eur J Pharmacol* 2008; **583**: 174–85.
- 63 Wang Z, Neylan TC, Mueller SG, Lenoci M, Truran D, Marmar CR, et al. Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. *Arch Gen Psychiatry* 2010; **67**: 296–303.
- 64 Chen MC, Hamilton JP, Gotlib IH. Decreased hippocampal volume in healthy girls at risk of depression. *Arch Gen Psychiatry* 2010; **67**: 270–6.
- 65 de Geus EJ, van't Ent D, Wolfensberger SP, Heutink P, Hoogendijk WJ, Boomsma DI, et al. Intrapair differences in hippocampal volume in monozygotic twins discordant for the risk for anxiety and depression. *Biol Psychiatry* 2007; **61**: 1062–71.
- 66 Prusoff BA, Merikangas KR, Weissman MM. Lifetime prevalence and age of onset of psychiatric disorders: recall 4 years later. *J Psychiatr Res* 1988; **22**: 107–17.
- 67 Wiener P, Alexopoulos GS, Kakuma T, Meyers BS, Rosenthal E, Chester J. The limits of history-taking in geriatric depression. *Am J Geriatr Psychiatry* 1997; **5**: 116–25.
- 68 Koolschijn PCMP, van Haren NEM, Lensvelt-Mulders GJLM, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp* 2009; **30**: 3719–35.

