

White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression

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Background

Cerebrovascular changes and glucocorticoid mediated hippocampal atrophy are considered relevant for depression-related cognitive deficits, forming putative treatment targets.

Aims

This study examined the relative contribution of cortisol levels, brain atrophy and white matter hyperintensities to the persistence of cognitive deficits in older adults with depression.

Method

Thirty-five people aged ≥ 60 years with DSM-IV major depression and twenty-nine healthy comparison controls underwent magnetic resonance imaging (MRI) and were followed up for 18 months. We analysed the relationship between baseline salivary cortisol levels, whole brain, frontal lobe and hippocampal volumes, severity of white matter hyperintensities and follow-up cognitive function in both groups by testing the interaction between the groups and these biological measures on tests of memory, executive functions and processing speed in linear regression models.

Results

Group differences in memory and executive function follow-up scores were associated with ratings of white matter hyperintensities, especially of the deep white matter and periventricular regions. Compared with healthy controls, participants with depression scoring within the third tertile of white matter hyperintensities dropped two and three standard deviations in executive function and memory scores respectively. No biological measure related to group differences in processing speed, and there were no significant interactions between group and cortisol levels, or volumetric MRI measures.

Conclusions

White matter hyperintensities, rather than cortisol levels or brain atrophy, are associated with continuing cognitive impairments in older adults with depression. The findings suggest that cerebrovascular disease rather than glucocorticoid-mediated brain damage are responsible for the persistence of cognitive deficits associated with depression in older age.

Declaration of interest

None.

Cognitive deficits affecting multiple cognitive domains are a core feature of depressive disorder at all ages.¹ In late-life depression (typically after age 60 years), these deficits have been shown to persist despite recovery from mood symptoms.^{2,3} Further, structural brain changes in late-life depression have been found to include volume reductions in the medial temporal lobe/hippocampus,^{4–6} frontal lobe^{7–9} and an increased prevalence of white matter hyperintensities.¹⁰ Several studies have shown that these cerebral changes relate to cognitive deficits in depression: hippocampal volume reductions have been associated with memory deficits^{5,6} and white matter hyperintensities have been associated with impaired memory,^{11–13} executive dysfunction^{11,14,15} and reduced processing speed.¹¹

However, the relationship between other biological changes in depression such as hypercortisolaemia and brain atrophy and cognitive impairment is less clear. Whereas excessive adrenal glucocorticoid secretion in rodent brains has been shown to lead to hippocampal cell death by excessive glutamate inflow,¹⁶ studies in humans have been inconclusive.⁵ In addition, few studies have examined which biological and cerebral changes have prognostic utility for the long-term persistence of cognitive impairments in late-life depression. We have previously shown that baseline measures of hippocampal volume predicted persistence of memory impairment after 6 months, whereas levels of cortisol did not.⁵ However, the role of white matter hyperintensities was not examined in that study, neither were relations with other cognitive domains.

The aim of the present study was to extend these initial findings to a longer observation period and to examine whether

other biological changes are associated with continuing cognitive impairments. We hypothesised that the worse cognitive functioning seen in older adults with depression relative to controls would be associated with more severe white matter hyperintensities and frontal and hippocampal volume reductions at baseline. Based on our previous findings,⁵ we expected hypercortisolaemia to play no role in the persistence of these deficits in the long term.

Method

Participants

Sixty-six people aged 60 and over with DSM-IV¹⁷ major depression were recruited from clinical old age psychiatry services covering geographically based catchment areas, and included referrals from day hospitals, in-patient units and out-patient clinics (depression group). The control group ($n = 36$) of older people (all over 60 years of age) with no current or past history of depression were recruited from community sources such as The Royal British Legion and spouses of patients attending the same hospital units. After complete description of the study to the participants, written informed consent was obtained. We excluded older adults with a history of prior cognitive impairment, history or evidence of stroke or transient ischemic attack or a Cambridge Cognitive Examination (CAMCOG)¹⁸ score of < 70 . Participants with severe or unstable physical illness (e.g. insulin-dependent diabetes mellitus, untreated hypothyroidism, uncontrolled heart failure, cancer) were excluded if their conditions were thought to affect

their ability to comply with the protocol or have a significant impact on survival that would interfere with completion of the follow-up study. Additional exclusion criteria were: history or current substance/alcohol misuse; long-term use (>2 months) of steroids during lifetime; use of steroid or other medication within the past 3 months thought to interfere with hypothalamic–pituitary–adrenal (HPA) axis; electroconvulsive therapy in past 3 months; use of medication thought to affect cognition (e.g. non-hypnotic benzodiazepines, antipsychotics, sedative tricyclic antidepressants or anticholinergic medication); and presence of other neurological diagnosis. Use of newer antidepressants (e.g. selective serotonin reuptake inhibitors and venlafaxine) and lithium was permitted, as were orally inhaled steroids. The study was approved by the local ethics committee and after a complete description of the study all participants gave written informed consent.

Assessment

Participants underwent a comprehensive assessment including psychiatric history, mental state and physical examination. Depression was diagnosed according to DSM–IV¹⁷ criteria and symptom severity rated with the Montgomery–Åsberg Depression Rating Scale (MADRS).¹⁹ Demographic information (including past and current medical and psychiatric history, medication taken, family history and education) and history of depressive episodes were collected from multiple sources to validate or enrich information from face-to-face interviews (e.g. case notes, general practitioner records and informant accounts to determine number of previous episodes, age at onset and total lifetime duration of depression). An extensive neuropsychological test battery was administered to consenting participants (detailed below). Participants were reassessed after 6 and 18 months; 93 (90%) and 78 (76%) participants were available for the extended examinations at 6 and 18 months respectively.

Neuropsychological assessment

The test battery was primarily designed to measure memory, processing speed and executive functions, as they represent core neuropsychological deficits in depression in older adults.¹ Tests used in the present study included both traditional pen and paper and computerised tasks.

- (a) The Rey Auditory Verbal Learning Test (AVLT),²⁰ a test of episodic memory. The three measures immediate recall, delayed recall and delayed recognition (number of correct positives) were used.
- (b) The FAS verbal fluency test,²¹ a task sensitive to frontal lobe impairment.
- (c) The Trail Making Test (TMT),²¹ a test of mental flexibility and divided attention.
- (d) The Stroop Colour Word Test (SCWT),²² a test for response inhibition and selective attention.
- (e) A computerised continuous performance task (VIGIL).²³ Over 8 min, participants have to press a button to a complex target stimulus (letter K when preceded by the letter A), presented 100 times within a total of 480 stimuli (displayed serially in a pseudo-random fashion). Errors of omission and commission can be used as a measure of vigilance and inhibition but in the present study only response latencies (in msec) were used as a measure of processing speed.

Salivary cortisol analysis

Cortisol levels were assessed by collecting saliva using Salivettes (Sarstedt, Nümbrecht, Germany). Participants chew on a cotton wool plug to produce saliva. Samples were collected at baseline at four time points (08.00 h, 12.00 h, 16.00 h, 20.00 h) over 3 consecutive days, followed by centrifugation and storage at -20°C until assayed. Salivary cortisol was measured using an ^3H disequilibrium assay, the radioactive cortisol for which was supplied by Amersham Health, Amersham, UK, the primary antibody Ab1002 and the solid phase anti-rabbit serum by IDS, Tyne and Wear, UK. The intra- and inter-assay coefficients of variation for 7.0, 47 and 87 nmol/l cortisol samples were 13.0 and 14.6%, 10.7 and 9.8%, 9.4 and 10.2% respectively. Average area under the curve (AUC) for the 3 days was calculated. Baseline cortisol data were available for 34 (94%) people in the control group and 42 (64%) participants in the depression group.

Magnetic resonance imaging (MRI) protocol and analysis

As described previously^{5,24} images were acquired using a 1.0 T Siemens Magnetom Impact Expert System (Siemens Medical, Erlangen, Germany). Whole brain T_1 -weighted three-dimensional magnetisation prepared rapid-acquisition gradient echo (3D-MPRAGE) turbo flash data-sets were acquired in the sagittal plane (repetition time (TR) = 11.4 msec, echo time (TE) = 4.4 msec, inversion time (TI) = 400 msec, flip angle 15° , matrix 256×256 , slice thickness 1 mm, cubic voxels of 1 mm) resulting in truly isotropic voxels of $1 \times 1 \times 1$ mm for optimal grey–white matter contrast. Axial dual spin echo sequences were also obtained to yield proton density and T_2 images. Proton density and T_2 images were yielded from RARE (rapid acquisition with relaxation enhancement) technique dual echo (TR = 2800 ms, TE = 14 (proton density) ms/85(T_2) ms, matrix 256×256 , field of view 230 mm, pixel size 0.92×0.92 mm, acquisition time 4 min 13 sec) sequences with axial slice thickness 5 mm and 0.5 mm gap. For volumetric analyses, T_1 images were then transferred to a Sun Ultra 10 work station running Solaris 2.7 (Sun Microsystems, Mountain View, California, USA). Hippocampal volume was analysed by a single operator (A.L.) who was masked to diagnosis using the AnalyzeAVW-3.0 software (AnalyzeDirect.com, Lenexa, Kansas, USA; Mayo Foundation Biomedical Imaging Resource, Rochester, Minnesota, USA). To ensure consistent slicing images were re-orientated along the long axis of the hippocampus (for regional demarcation see O'Brien *et al*).⁵ Whole brain volume was analysed by a semi-automated iterative process of erosion and region-growing. Hippocampal volume was normalised by dividing it by whole brain volume and multiplied by 1000 for convenience of presentation. Whole-brain normalised frontal lobe volume (factor 1000) was analysed with the Medical Information Display and Analysis System (MIDAS-3.0) and analysed by a single operator (O.P.A.) as described previously (Almeida *et al*).⁸ White matter hyperintensities were rated visually from the axial dual echo scans by two experienced raters (R.B. and J.T.O.) using the well-established Scheltens scale.²⁵ This can provide a measure of overall severity of white matter hyperintensities by summing scores for the four regions covered by the scale (periventricular, deep white matter, basal ganglia and infratentorial) on the rating scale. Severity in white matter hyperintensities could be successfully rated in 27 (75%) people in the control group and 51 (76%) in the depression group. Magnetic resonance images of brain volumes could be successfully analysed in 35 (97%) controls and 51 (76%) individuals with depression.

Statistical analysis

Neuropsychological test scores were standardised in relation to the controls. An overall memory *z*-score was created by adding up the AVLT *z*-scores of immediate recall, delayed recall and delayed recognition, and this 'compound memory score' was again standardised. Similarly, an overall executive functions *z*-score was created by adding up the *z*-scores of verbal fluency, TMT difference A–B and SCWT correct responses. As a result, we produced three summary measures of cognitive function, with higher scores indicating better performance: memory, executive functions and processing speed (VIGIL latencies). We analysed the impact of our biological measures on the difference in cognitive outcome between the control group and the depression group by testing the interaction between group (0, control group; 1, depression group) and the biological measures on the neuropsychological *z*-scores. Analyses were adjusted *a priori* for age, gender and years of education. The alpha-level was fixed at $P < 0.05$ and all statistical tests reported are two-tailed. In addition, we report *P*-values derived from Simes' modification of the Bonferroni correction in order to control for multiple testing.²⁶ Simes' procedure is less conservative than traditional Bonferroni correction and is therefore considered superior if outcomes are correlated with each other, as in this study. A test is considered significant if the observed *P* is lower than Simes' adjusted significance level. All analyses were performed on STATA 10.1 for Windows.

Results

At 18 months, 45 out of 66 (68%) people in the depression group were available for assessment, of which none met DSM–IV criteria for dementia. Of those lost to follow-up (Fig. 1), 19 withdrew consent and 3 died. There were no differences between participants available and not available for follow-up in relation to age ($t = 0.10$, d.f. = 65, $P = 0.919$), gender ($\chi^2 = 0.07$, d.f. = 65, $P = 0.797$), years of education ($t = -0.17$, d.f. = 65, $P = 0.785$), age at onset ($t = -0.04$, d.f. = 65, $P = 0.972$), MADRS score (baseline: $t = -1.47$, d.f. = 65, $P = 0.147$; 6 months: $t = 0.34$, d.f. = 55, $P = 0.739$) or remission status (baseline: $\chi^2 = 0.53$, d.f. = 65, $P = 0.466$; 6 months: $\chi^2 = 1.04$, d.f. = 55, $P = 0.308$). Similarly, there were no differences between individuals in the depression group who were or were not available for follow-up on *z*-scores for memory (baseline: $t = 1.12$, d.f. = 32, $P = 0.270$; 6 months: $t = 1.11$, d.f. = 49, $P = 0.274$), executive functions (baseline: $t = 1.19$, d.f. = 35, $P = 0.241$; 6 months: $t = 1.87$, d.f. = 49, $P = 0.067$) or processing speed (baseline: $t = 0.83$, d.f. = 28, $P = 0.414$; 6 months: $t = 0.72$, d.f. = 44, $P = 0.478$). Finally, there were no differences between these two groups on cortisol concentration ($t = 0.82$, d.f. = 40, $P = 0.415$), whole brain volume ($t = -1.78$, d.f. = 49, $P = 0.082$), hippocampal volume ($t = 0.10$, d.f. = 49, $P = 0.921$), frontal lobe volume ($t = -0.07$, d.f. = 49, $P = 0.942$) or overall white matter hyperintensities ($t = -0.67$, d.f. = 49, $P = 0.508$).

Baseline MRI data and follow-up neuropsychological test scores were available for 35 people in the depression group and 29 people in the control group. Individuals in the depression group on average had fewer years of formal education and higher depression scores at baseline and follow-up compared with those in the control group (Table 1). They performed worse on all neuropsychological tests at follow-up and had higher AUC cortisol levels at baseline, but there were no significant differences in total, frontal or hippocampal brain volume and overall white matter hyperintensities.

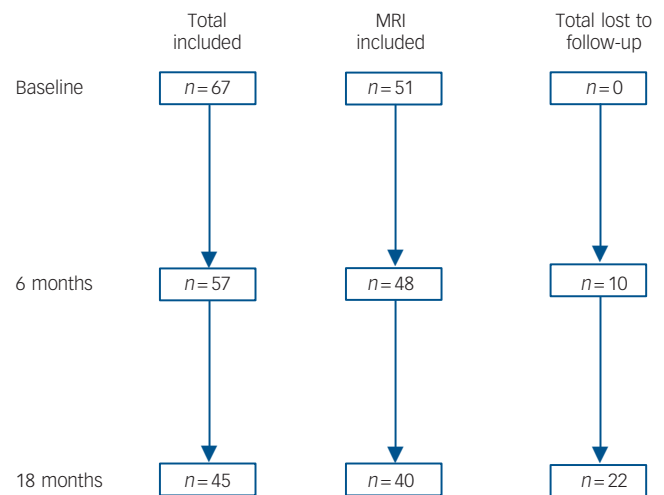


Fig. 1 Flow chart illustrating loss to follow-up and numbers of participants retained in the total sample and those who had baseline magnetic resonance imaging (MRI).

Impact of biological measures on group differences in neurocognitive function

Tests for interactions between group and biological measures on neurocognitive outcome adjusted for age, gender and years of education are summarised in Table 2. Differences in memory *z*-scores at 18 months between the depression group and the control group were not moderated by cortisol levels or volumetric measures, but showed a significant interaction with overall white matter hyperintensities. With every one-point increase in white matter hyperintensities severity, the score on memory declined by 0.21 standard deviations in individuals with depression. Likewise, there were no significant interactions between group and cortisol levels or volumetric measures on executive function *z*-scores, but yet again there was a significant interaction with overall white matter hyperintensities (decline of 0.18 standard deviations with every one-point increase in white matter hyperintensities severity). Both effects remained significant when multiple testing was controlled for. In contrast, group differences in processing speed were not moderated by any biological measure.

Further explorations into the role of white matter hyperintensities

In order to clarify the role of white matter hyperintensities further, we investigated potential dose–response relations between white matter hyperintensities severity and neurocognitive outcome by dividing the overall severity rating into tertiles. There were significant interactions between group and white matter hyperintensities tertiles on memory and executive function scores that showed evidence of an effect gradient (Fig. 2). Using the healthy controls within the first tertile (no/minor white matter hyperintensities, $n = 10$) as the reference group, individuals with depression within the same tertile ($n = 11$) did not differ in memory scores (*z*-score difference with reference group: -0.18 , 95% CI -1.41 to 1.06 , $P = 0.775$). However, being depressed within the second white matter hyperintensities tertile ($n = 11$) was associated with a decline of two standard deviations in memory (*z*-score difference with reference group: 2.21 , 95% CI -3.68 to -0.74 , $P = 0.004$; test for interaction of group and white

Table 1 Differences in demographic and clinical characteristics between the healthy control group and the depression group who had data available from baseline magnetic resonance imaging or cortisol and follow-up neuropsychological testing

	Depression group (n=35)	Healthy control group (n=29)	Analysis		
			Test statistic	d.f.	P
Age, years: mean (s.d.)	74.1 (6.5)	72.8 (6.9)	$t = -0.81$	62	0.422
Female: n (%)	28 (80)	22 (76)	$\chi^2 = 0.16$	62	0.690
Education, years: mean (s.d.)	9.4 (2.0)	10.6 (2.2)	$t = 2.14$	62	0.037
Montgomery-Åsberg Depression Rating Scale at baseline, mean (s.d.)	20.6 (9.8)	2.0 (2.1)	$t = -10.01$	62	≤ 0.001
Montgomery-Åsberg Depression Rating Scale at 18 months, mean (s.d.)	8.0 (10.2)	1.6 (2.0)	$t = -3.32$	62	0.002
Illness duration, weeks: mean (s.d.)	58.3 (56.0)				
Number of episodes, mean (s.d.)	3.6 (3.2)				
Antidepressant use, n (%)	28 (80)				
Memory at 18 months, mean (s.d.)	-1.7 (2.1)	0.1 (0.9)	$t = 4.19$	62	≤ 0.001
Executive functions at 18 months, mean (s.d.)	-1.3 (1.8)	0.0 (1.0)	$t = 3.26$	60	0.002
Processing speed at 18 months, mean (s.d.)	-0.7 (1.2)	0.1 (1.0)	$t = -2.71$	58	0.009
Cortisol at baseline, mean (s.d.)	158 (80)	100 (24)	$t = -3.63$	43	≤ 0.001
Whole brain volume (in mm ³), mean (s.d.)	965 (81)	969 (88)	$t = 0.20$	61	0.844
Left + right raw frontal volume (in mm ³), mean (s.d.)	96 (16)	98 (14)	$t = 0.52$	62	0.609
Left + right normalised frontal volume, ^a mean (s.d.)	92 (12)	92 (7)	$t = 0.07$	62	0.944
Left + right raw hippocampal volume (in mm ³), mean (s.d.)	5.6 (0.9)	5.8 (0.8)	$t = 0.55$	61	0.583
Left + right normalised hippocampal volume, ^b mean (s.d.)	5.8 (0.7)	5.9 (0.5)	$t = 0.63$	61	0.533
Overall white matter hyperintensities, mean (s.d.)	12.2 (5.4)	13.2 (9.9)	$t = 0.47$	53	0.642

a. Measured as (left + right raw frontal volume/whole brain volume) × 1000.
b. Measured as (left + right raw hippocampal volume/whole brain volume) × 1000.

Table 2 Interactions between baseline biological measures and group (0, healthy control group; 1, depression group) on neurocognitive outcomes at 18 months

	z-scores								
	Memory			Executive function			Processing speed		
	Interaction by group	95% CI	P	Interaction by group	95% CI	P	Interaction by group	95% CI	P
Cortisol	0.01	-5.17 to 1.12	0.505	-0.01	-0.04 to 0.01	0.288	0.01	-0.01 to 0.02	0.393
Whole brain volume	0.00	-0.01 to 0.01	0.593	0.00	-0.01 to 0.01	0.709	0.00	-0.00 to 0.01	0.575
Frontal lobe volume	-0.03	-0.14 to 0.09	0.636	-0.05	-0.15 to 0.04	0.279	-0.02	-0.10 to 0.05	0.554
Hippocampal volume	0.47	-1.00 to 1.95	0.521	0.94	-0.36 to 2.24	0.153	0.16	-0.82 to 1.14	0.741
Overall white matter hyperintensities	-0.21	-0.32 to -0.10	$\leq 0.001^a$	-0.18	-0.29 to -0.06	0.004 ^b	-0.03	-0.12 to 0.05	0.460

a. <Simes' significance level for multiple testing: $\alpha_{\text{Simes}} = 0.003$. Results remain statistically significant if the observed P is smaller than α_{Simes} .
b. <Simes' significance level for multiple testing: $\alpha_{\text{Simes}} = 0.007$. Results remain statistically significant if the observed P is smaller than α_{Simes} .

matter hyperintensities tertile (first v. second): $b = -2.04$, 95% CI -3.92 to -0.14 , $P = 0.36$). Being depressed in the third white matter hyperintensities tertile ($n = 11$) went together with a decline of three standard deviations (z-score difference -3.23 , 95% CI -4.56 to -1.91 , $P = 0.001$; test for interaction of group and white matter hyperintensities tertile (first v. third): $b = -3.06$, 95% CI -4.84 to -1.27 , $P = 0.001$). For executive functions, neither the participants with depression within the first white matter hyperintensities tertile group (z-score difference -0.28 , 95% CI -1.45 to 0.91 , $P = 0.643$) nor those within the second white matter hyperintensities tertile differed from the reference group (z-score difference -0.77 , 95% CI -2.18 to 0.64 , $P = 0.276$; test for interaction: $b = -0.50$, 95% CI -2.31 to 1.31 , $P = 0.583$). Only white matter hyperintensities within the third tertile were associated with worse executive functions scores in participants with depression (z-score difference -2.40 , 95% CI -3.72 to -1.08 , $P \leq 0.001$; test for interaction: $b = -2.12$, 95% CI -3.86 to -0.39 , $P = 0.018$).

In order to clarify the role of the anatomical location of white matter hyperintensities, the continuous overall severity rating was divided into its constituent parts: deep white matter hyperintensities, periventricular white matter hyperintensities, basal ganglia hyperintensities and infratentorial hyperintensities. Adjusted analyses showed that group difference in memory z-scores were moderated by deep (test for interaction: $b = -0.30$, 95% CI -0.47 to -0.13 , $P \leq 0.001$) and periventricular white matter hyperintensities (test for interaction: $b = -0.68$, 95% CI -1.21 to -0.15 , $P = 0.014$), but not basal ganglia (test for interaction: $b = -0.07$, 95% CI -0.50 to 0.35 , $P = 0.729$) or infratentorial hyperintensities (test for interaction: $b = -0.32$, 95% CI -1.07 to 0.43 , $P = 0.398$). Group differences in executive functions were moderated by deep white matter hyperintensities (test for interaction: $b = -0.21$, 95% CI -0.40 to -0.02 , $P = 0.027$), but not periventricular white matter hyperintensities (test for interaction: $b = -0.46$, 95% CI -0.99 to 0.06 , $P = 0.082$), basal ganglia (test for interaction: $b = -0.07$, 95% CI -0.46 to 0.32 , $P = 0.708$) or infratentorial

hyperintensities (test for interaction: $b = -0.39$, 95% CI -1.07 to 0.30 , $P = 0.260$).

Discussion

Main findings

In the present study, we found robust associations between ratings of white matter hyperintensities and neurocognitive impairment among older people with depression who were followed up for 18 months. More severe white matter lesions, especially in the deep white matter and periventricular regions, were associated with greater deficits in memory and executive functions at follow-up compared with a healthy control group. In contrast, whole or regional brain volume, including the hippocampus, and baseline cortisol levels were unrelated to persisting cognitive deficits. Further, white matter hyperintensities predicted cognitive deficits in people with depression but were unrelated to cognitive performance in healthy controls. This confirms earlier reports¹⁵ and is in line with studies showing that white matter lesions are commonly present in the brains of healthy older adults, where they do not necessarily relate to poor cognitive outcome.²⁷ Several mechanisms might explain this. First, individuals with depression might have lowered brain reserve to compensate for the damage exerted by white matter hyperintensities as a result of the effects of accumulated genetic and environmental risk exposure. As a consequence, the additional burden placed by white matter hyperintensities gives rise to cognitive deficits in this group. Alternatively, the neuropathology of white matter hyperintensities

might be different in depression compared with normal ageing. Indeed, previous work has shown that white matter hyperintensities in depression are more often ischaemic in nature.²⁸ Third, the strategic anatomical lesion location, and consequently the neurocircuits disrupted, might differ between the groups. Late-life depression is particularly associated with deep white matter lesions affecting projection to and from the frontal lobes, thereby disrupting circuits for cognitive and emotional control, leading to depressive symptoms and executive dysfunction.¹⁵

Our findings are consistent with previous cross-sectional reports showing total brain hyperintensities correlate with impaired episodic memory^{11–13} and executive functions in older people with depression.^{11,14,15} In a recent report we found patients' deficits in individual cognitive domains to be stable from baseline to 6 and 18 months,²⁹ thus suggesting that white matter hyperintensities contribute to the persistence of cognitive dysfunction observed among some older people with depression. These findings are consistent with the vascular hypothesis of depression,³⁰ and indicate that white matter hyperintensities and cerebrovascular disease play an important role in the phenotypic expression of depression in later life.^{10,28} The aetiological relevance of vascular factors in the onset or recurrence of depression has been implicated by research showing that white matter hyperintensities can pre-date the onset of depression,^{31,32} and are likely to further progress over time in people with prevalent depression.³² In addition, more severe white matter changes have been associated with worse prognosis of depression, including poor response to antidepressant treatment,^{33,34} chronic and relapsing course,³⁵ an increased risk for dementia and higher mortality.³⁶ These findings have led to the consideration of 'vascular depression' as a distinct diagnostic subtype in the upcoming DSM-V associated with old age, white matter hyperintensities, late onset and deficits in executive functions.³⁷ Recently, Sneed and colleagues, using latent class analysis, reported that the presence of deep white matter lesions has almost perfect discriminating ability for distinguishing classes of vascular and non-vascular depression.³⁸ Our study adds that such white matter hyperintensities have predictive validity as they are associated over 18 months with poorer memory and executive functions. However, the predictive validity of white matter hyperintensities for treatment response, clinical and other cognitive outcomes has to be clarified further before any criteria of vascular depression can be recommended for use in regular clinical practice.

The present study provides important evidence that although white matter hyperintensities are associated with key cognitive outcomes, other biological abnormalities, including hypercortisolaemia, are not. Despite evidence for a toxic effect of chronic glucocorticoid hypersecretion on hippocampal neurons in animal models¹⁶ and humans,³⁹ we found no effect of baseline cortisol levels or hippocampal volume on differences between participants with depression and healthy controls in follow-up neurocognition. As we reported previously, cortisol levels are further not associated with hippocampal volume or baseline memory function.⁵ In another report using this same sample, we found that participants with a late onset but not an early onset had reduced hippocampal volume,²⁴ which has been replicated by other volumetric studies^{6,40} and contradicts the idea that cumulative (lifetime) cortisol exposure is sufficient to explain hippocampal damage in depression. We acknowledge that our results are not consistent with some reports in younger people with depression⁴¹ and thus suggest that in older people with depression pathogenic mechanisms other than hypercortisolaemia might explain hippocampal volume loss and associated memory deficits, including vascular pathology.

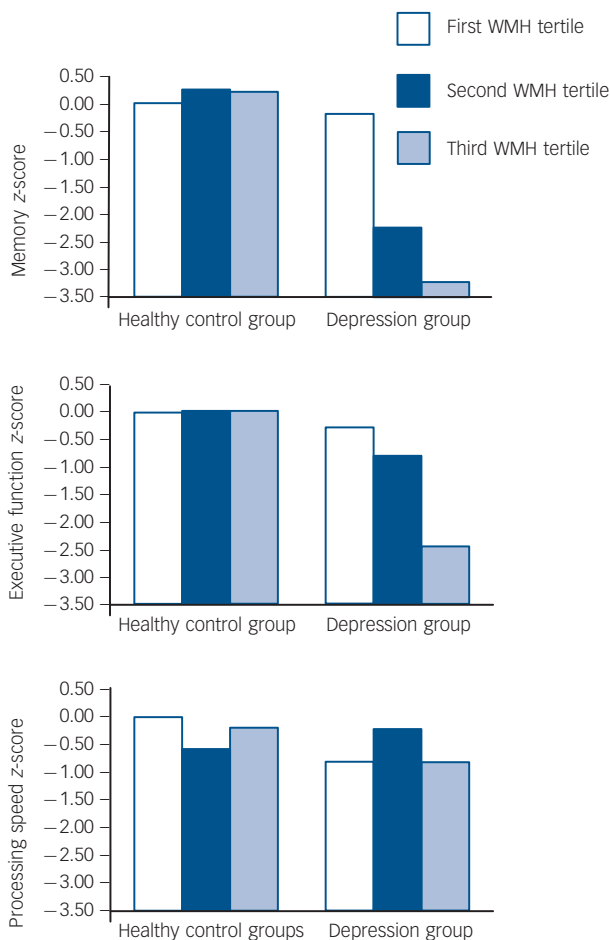


Fig. 2 Differences in neurocognition across groups and across tertiles of white matter hyperintensities (WMH).

Strengths and weaknesses

Notable strengths of this study are a comprehensive assessment of biological parameters that have been suggested to have an impact on cognitive functioning in depression, a relatively long follow-up duration, the assessment of core cognitive domains, and the inclusion of a matched-comparison group of healthy participants that was followed-up in parallel. Yet, some methodological aspects deserve attention. Magnetic resonance image analyses of different regions of interest were performed using different software packages, although correlations of whole brain volumes obtained using both packages was very high ($r=0.91$). Ratings of white matter hyperintensities were based on visual rather than volumetric data, although this approach has been shown to be reliable and to have good face validity.²⁴ Salivary cortisol is a measure with high variability, so that the absence of an effect on cognition might relate to levels not accurately reflecting average HPA axis function in a participant. However, we attempted to reduce that variability by measuring cortisol at four time points over 3 days at each time point, and used the average AUC to gain a measure of overall cortisol output. In addition, we did not find an association between hippocampal volume and cognition, which further undermines the relevance of cortisol-induced brain changes. It would have further been interesting to look at the relevance of white matter hyperintensities on cognition as a function of age at onset since vascular changes have been found to relate to late-onset depression in particular.¹⁰ Unfortunately, we were unable to explore this further given the small cell sizes that would have resulted from stratification by age at onset. However, there were no significant differences in the number of early-onset or late-onset participants across white matter hyperintensities tertiles in a *post hoc* analysis (highest white matter hyperintensities tertile: early-onset depression, 4 (22%); late-onset depression, 7 (47%); Fisher's exact $P=0.292$).

Implications

In conclusion, white matter hyperintensities moderate the severity of continuing cognitive deficits in older people with depression in a dose-response fashion. In contrast, high levels of cortisol and hippocampal volume loss do not appear to play a major role in the persistence of depression-related cognitive deficits. Our results suggest a need to find effective treatment strategies for these deficits which remain following successful treatment of mood symptoms.

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Poems
by
doctors

Today I do not want to be a doctor

Today I do not want to be a doctor.

No one is getting any better.

Those who were well are sick again
And those who were sick are sicker.

The dying think that they will live.
And the healthy think they are dying.

Someone has taken too many pills.
Someone has not taken enough.

A woman is losing her husband.
A husband is losing his wife.

The lame want to walk.
The blind want to drive.
The deaf are making too much noise.
The depressed are not making enough.

The asthmatics are smoking.
The alcoholics are drinking.
The diabetics are eating chocolate.

The mad are beginning to make sense.

Everybody's cholesterol is high.

Disease will not listen to me.

Even when I shake my fist.

Glenn Colquhoun was born in Auckland, New Zealand and is a doctor practising on the Kapiti Coast, near Wellington. He was the winner of the 2003 Montana New Zealand book award for poetry. This poem is from *Playing God*, published by Steele Roberts in New Zealand and Hammersmith Press in London.

Poem selected by Femi Oyeboode.

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