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White matter hyperintensities in late life depression: a systematic review

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► The appendix is published online only at http://jnnp.bmj.com/content/vol79/issue6

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Received 9 May 2007
Revised 26 July 2007
Accepted 8 August 2007
Published Online First 23 August 2007

ABSTRACT

Background: White matter hyperintensities in MRI scans are age related but appear to be more prevalent in depressed patients. They may be more pronounced in late onset depression. This finding, if confirmed, would potentially illuminate the heterogeneity of depression in elderly subjects.

Methods: We conducted a systematic literature search of studies investigating white matter changes in late life depression, identifying 98 studies. The 30 remaining eligible studies were scrutinised for the presence and severity measures of periventricular and deep white matter changes in late life, late onset and, if available, early onset depression as well as in controls. Comparisons between groups were entered into random effects meta-analyses using odds ratios and Cohen's d, as appropriate. Correlations with potential confounders, such as age difference between groups, were explored.

Results: Late life depression and, to a greater extent, late onset depression in late life were characterised by more frequent and intense white matter abnormalities. In particular, the odds of having white matter changes were over 4 for late compared with early onset depression. Similarly, on severity scales, late onset depression had scores of 0.7–0.8 standard deviations above early onset patients.

Conclusions: Significant differences between early and late onset depression suggest different aetiological mechanisms, in accordance with a theory of "cerebrovascular" depression of late onset. Greater duration of depressive symptoms, signs and treatment does not appear to have a measurable impact on white matter signal in MRI scans.

Depression in late life (LLD) is a common[1] and heterogeneous illness characterised by diverse aetiological factors[2] that are poorly understood.[3] While psychosocial and genetic factors play a primary causal role in the occurrence of depression in early life,[4] this is not necessarily the case for depression arising in later life. Evidence suggests that the importance of genetic predisposition to affective disorders declines in geriatric depression,[5 6] and may be replaced by associations with structural abnormalities of the brain.[7 8] In line with this, CT and MRI studies have demonstrated pathological changes in the brains of patients presenting with LLD.[9–14]

White matter hyperintensities and depression

White matter hyperintensities (WMHs) are areas of increased signal intensity that become apparent, particularly on T2 weighted MRIs. As hyperintense lesions are strongly associated with increasing age,[15] it is not surprising that hyperintensities are commonly reported in healthy elderly patients.[15–17] Importantly, however, a large number of studies have found a higher rate and severity of WMHs in individuals with LLD compared with healthy elderly controls.[13 14 18–21] A number of explanations have been advanced: underlying pathological processes predispose elderly individuals to the development of both depression and WMHs,[20] or depression and its treatment cause the development of WMHs.[20 22] Many patients with LLD have received long term antidepressant medications; potential cerebrovascular side effects could cause episodes of subclinical cerebral ischaemia that might result in WMHs.[10 21] Individuals with early onset depression (EOD), who by definition have experienced a longer duration of illness, should then demonstrate more severe WMHs than individuals with late onset depression (LOD).

The dominant view is that WMH signals occur in a subgroup of patients with geriatric depression and reflect an underlying condition (ie, cerebrovascular disease) that predisposes individuals to the development of depression[20 23 24] by disrupting fibre tracts connecting cortical and subcortical structures (eg, frontostriatal circuits). Consistent with this hypothesis, LLD is also associated with pronounced deficits in processing speed and executive functions (for a recent review Herrmann and colleagues[25]).

Additional support for the cerebrovascular hypothesis comes from findings that in *both depressed and non-depressed* individuals, WMHs are highly associated with cerebrovascular risk factors, in particular hypertension,[11 17 18 26 27] but also diabetes, history of myocardial infarction or coronary artery disease, and smoking.[11 28] Moreover, neuropathological studies show that WMH are characterised by arteriosclerosis, perivascular demyelination, dilated periventricular spaces, vascular ecstasia, ischaemia, incomplete infarction and infarction with necrosis.[29 30]

A variety of authors have reported that increased severity of hyperintense lesions is related to a more chronic course of depression,[31–33] poorer response to antidepressant medication[34–36] and long term disability.[32] In addition, although some studies failed to find an association of WMHs with cognition,[37] others reported that WMHs are related to cognitive decline in various domains, particularly executive skills, attention and mental speed.[27 34 38 39] It thus appears that WMHs are also of clinical significance in LLD.

Consistent with the natural history of cerebrovascular disease, the vascular depression hypothesis predicts a late age of onset.[36] WMH signals should therefore be more severe in LOD compared with EOD, be associated with recent onset of depression and increase more rapidly in LOD than EOD over time. However, there are various studies that have failed to show a difference between LOD and EOD in rate and severity of WMHs,[1 8 40–43] and the nature of confounding factors related to the presence or absence of WMHs in LLD is unclear.

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Aims and hypotheses

In the advent of more sophisticated methods to study white matter integrity, we felt that a quantitative review and meta-analysis of the studies of WMH signals in late life and particularly in late onset depression was timely. Such a quantitative review should inform the hypotheses to be tested in new studies of diffusion tensor MRI. We examined and compared both the severity and presence of WMH signals in individuals with geriatric depression (LOD and EOD) and healthy elderly controls.

To our knowledge, no previous study has attempted to quantify the differences in WMH presence and severity between these groups. Our hypothesis was that individuals with geriatric depression would demonstrate greater WMH signals than healthy controls. Our secondary hypothesis was that, consistent with a cerebrovascular causation of LOD, WMH would be more common and severe in individuals with LOD compared with EOD.

METHODS

Data acquisition

We conducted a systematic review and meta-analysis following published guidelines.[44] Studies investigating white matter lesions in geriatric depression were retrieved systematically from Medline and Embase, and reference lists of these publications were scanned for additional relevant studies. The search was completed by the first author (LLH, research assistant) in January 2007 using the search terms ((''depression'' OR ''depressed'') AND (''geriatric'' OR ''late life'' OR ''old age'' OR ''late onset'' OR ''elderly'' OR ''older'') AND (''connectivity'' OR ''white matter'' OR ''grey matter'' OR ''gray matter'' OR ''MRI'' OR ''magnetic resonance imaging'')). Only studies published in English between 1966 and January 2007 were included.

Studies were included if they were of cross sectional design, included a sample of patients with LLD or LOD *and*, for comparison, either healthy controls or a sample of patients with EOD, or both. Where there was an overlap in samples between studies, we chose to include the study with the most participants or providing more detailed results. In order to be included in this review, patients and controls were required to have a mean age of at least 55 years of age. Furthermore, depressed patients were required to meet the diagnostic criteria of major or minor unipolar depression according to DSM-III-R/DSM-IV. Implicitly, patients included in this review were not suffering from substance or medication abuse, general medical conditions or dementia.

The following variables were recorded in a systematic fashion: (i) demographic data, including age and age of onset, (ii) data on the presence of periventricular and deep WMHs and (iii) severity scores (mean ratings or mean lesion volumes) of periventricular or deep WMHs. Means (SD) of severity measures had to be available or derivable. If not available, the authors of studies published within the past 6 years were contacted and asked to provide these data. For severity ratings, the data were organised into three categories representing absent/mild, moderate and large WMHs. For studies that did not provide severity scores, these scores were calculated manually using the severity ratings if available. Studies that provided volumetric data only were not included in any of the categorical analyses.

Statistical analysis

Demographic variables were analysed by univariate ANOVA. The meta-analyses were done with StatsDirect (V.2.4.5. 30/05/2005). In order to assess differences in WMH severity scores, we used Cohen's d as a measure of effect size. Differences were regarded as significant when the 95% confidence interval (CI) did not include zero. In order to combine the severity of WMH signals in several studies, a random effect meta-analysis of Cohen's d was chosen. This method is more appropriate than the fixed effects model when there is a high degree of heterogeneity.[45] Variability of effects between the studies was investigated using as a test for heterogeneity, the Q (''non-combinability'' for d+) test. For data where there were clearly identifiable binary categories, or where such categories could be generated by splitting 4 grade scales (absent or minimal versus moderate to large WMHs), we also carried out a χ^2 analysis (random effects, DerSimonian-Laird) with 1 degree of freedom. This non-parametric test has the advantage that it is robust and not affected by the presence of outliers. Cochran Q was computed to test for non-combinability of the data.

RESULTS

Literature search

Our literature search identified a total of 98 studies which were subsequently scanned for inclusion/exclusion by LLH. A complete list of studies identified is available on request. After excluding studies that were not of a geriatric nature or did not examine WMH differences between patients with LLD and healthy controls, 47 structural MRI studies remained for inclusion. Of these, 14 studies were excluded from the analyses because of overlapping study samples. Thus a total of 30 studies reporting WMH prevalence or severity scores of patients with LLD remained. Overall, 20 of the 30 studies provided data relating to differences between patients with LLD and healthy controls (10 of these also specified numbers of LOD), whereas 20 studies examined WMHs in patients with LOD. Of these, five did not contain any patients with EOD, 10 only compared LOD with EOD and five included subjects with LOD and EOD in addition to controls.

Conversion to a WMH rating scale common scale

The majority of studies (n = 15) used the Fazekas/Coffey criteria in order to rate participants' WMHs. Here, periventricular WMHs are classified as (0) absent, (1) caps or pencil-thin lining, (2) smooth halo or (3) irregular periventricular hyperintensities extending into the deep white matter. For the purpose of our study, we grouped together grades (0) and (1) to represent ''absent or minimal periventricular hyperintensities'' and grades (2) and (3) to represent ''moderate to large periventricular hyperintensities''. According to the Fazekas/Coffey criteria, deep WMHs can be classified as (0) absent, (1) small foci, (2) becoming confluence of foci and (3) large confluent areas. Again, we combined grades (0) and (1) to represent ''absent or minimal deep WMHs'' and grades (2) and (3) to represent ''moderate or large WMHs''. The remaining studies used the Scheltens rating system (n = 4), their own rating system (n = 6), Zimmerman/Meguro criteria (n = 1), volumetric data (n = 2) or a simple ''absent/present'' system with no further comment (n = 2). For those studies that provided categorical data that could be converted to our own rating system, details of rating systems together with information on how those ratings were converted can be found in table 1.

Participant characteristics

Comparison between LLD and healthy controls

Mean ages of patients with LLD ranged from 60.96 to 76.0 years, with a mean of 70.9 years. Control participants were, on average, 69.7 years old (range 61.1–77.7). Very few

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Table 1 Rating scales and conversion to a common scale

Study	Scale and description	Conversion to categorical rating system
Krishnan *et al* (1988)[46]	(1) Absent	(1) Absent or minimal
Figiel *et al* (1991)[47]	(2) Present	(2) Moderate or large
Harrell *et al* (1991)[37]	(1) Absent	(1)–(3) Absent or minimal
	(2) Punctate lesions	(4)–(6) Moderate or large
	(3) Thin bands along lateral ventricles	
	(4) Smooth caps at tip of lateral ventricle	
	(5) Same as (4) but with stripes >2 mm	
	(6) Thick irregular caps and thick irregular stripes	
Churchill *et al* (1991)[40]	(1) Absent	(1) Absent or minimal
	(2) One or more foci in the white matter of the subcortical nuclei	(2) Moderate or large
Fujikawa *et al* (1993)[48]	(1) Lesions <5 mm^2	(1) Absent or minimal
	(2) Lesions >5 mm^2	(2) Moderate or large
Krishnan *et al* (1993)[8]	(0) Absent	(0)–(1) Absent or minimal
	(1) One subcortical hyperintensity	(2)–(3) Moderate or large
	(2) 2–5 subcortical hyperintensities	
	(3) >5 subcortical hyperintensities	
Lesser *et al* (1996)[27]	(1) Minimal (<1 cm2)	(1) Absent or minimal
	(2) Moderate (1–10 cm2)	(2)–(3) Moderate or large
	(3) Large (>10 cm2)	
Janssen *et al* (2007)[49]	(1) No lesions	(1)–(2) Absent or minimal
	(2) Small lesions (<3 mm)	(3) Moderate
	(3) Large lesions (>3 mm)	

studies reported the mean age of onset of their LLD participants (n = 6; mean 57.6 years (range 43.0–66.5)).

Comparison between LOD, EOD and healthy controls

Studies varied substantially in terms of age cut-offs used to define LOD, with cut-offs varying from 45 to 65 years of age. Mean ages for individuals with LOD, EOD and healthy controls were 71.7 years (range 63.1–77.6), 65.5 years (range 56.7–73.8) and 70.3 years (range 64.4–77.7), respectively. For more detailed information regarding demographic variables of study samples, see the appendix (published online).

Heterogeneity of recruitment sources of healthy controls

Some authors specifically tried to match their control participants to the depressed patients (eg, by selecting spouses or relatives of patients and thereby ensuring similar socioeconomic status and education); others recruited controls who had previously been referred for MRI scanning and who were subsequently selected on the basis of their normal scans. The vast majority of studies, however, recruited their controls from the community. Unfortunately, studies were rather vague about the exact source of recruitment within the community, such that this method could have either generated a sample of normal controls (ie, when taking a random sample of people from the community) or a sample of so called "super-normals" (ie, when selectively approaching individuals who may in some way be more educated or have a higher socioeconomic status, as is the case when recruiting people from societies or voluntary organisations).

Presence of WMH

The results of the odds ratio meta-analysis indicate that both periventricular and deep WMHs are significantly more common in LLD than in healthy age matched controls (table 2). In particular, the odds of showing periventricular WMHs on MRI are 2.15 times greater in patients suffering from late life depression than in healthy controls ($p<0.001$). Similarly, the odds of having deep WMHs are 1.92 times greater in patients with LLD than in controls ($p<0.01$).

When examining WMHs in LOD specifically, the likelihood that WMHs are present on MRI screens increases. It appears that in this patient group the odds of having periventricular hyperintensities are 2.57 times greater than in healthy controls (<0.001) and 4.51 times greater than in patients with EOD ($p<0.001$). Similarly, the odds of demonstrating deep WMHs are 2.64 times greater in patients with LOD than in healthy controls ($p<0.05$) and 4.33 times greater in LOD than in EOD ($p<0.001$).

While variability in studies comparing periventricular WMC between all diagnostic groups and deep white matter changes between LOD and EOD did not exceed a degree expected by chance, the studies comparing late life and late onset depression with controls had significant tests for heterogeneity, suggesting that systematic differences existed between studies.

WMH severity scales

Patients with LLD demonstrated significantly more severe WMHs than healthy control subjects (table 2), both in terms of periventricular (d = 0.6) and deep (d = 0.39) white matter. As several authors did not provide any data on severity of periventricular and deep WMHs separately, we also examined differences between groups with regard to combined (deep *and* periventricular) hyperintensities. As before, the difference between LLD and healthy controls reached statistical significance (d = 0.36).

Similar to the findings regarding prevalence, examining patients with LOD separately from patients with EOD appeared to result in increased effect sizes. Compared with healthy controls and patients with EOD, patients with LOD display significantly more severe hyperintensities in periventricular (d = 0.9 and d = 0.73), deep (d = 0.46 and d = 0.87) and combined (d = 0.44 and d = 0.73) white matter, respectively.

Between studies variability did not exceed chance for comparisons between LOD and EOD for deep and periventricular WMC, as well as LOD and controls for deep and combined

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Table 2 Presence and severity of white matter hyperintensities

Presence and absence of WMH (grouped as absent or minimal vs moderate or large)				Severity of WMH		
Location	n	Odds ratio (95% CI)	$Q\chi^2$	n	Cohen's d (95% CI)	Qd
Periventricular WM						
LLD/controls	11 (472/510)	2.15 (1.5–3.1)***	13.3	13 (535/364)	0.60 (0.3–0.9)	40.3***
LOD/controls	5 (183/296)	2.57 (1.6–4.2)***	4.0	5 (198/143)	0.90 (0.3–1.5)	26.1***
LOD/EOD	5 (133/87)	4.51 (2.2–9.2)***	4.5	6 (158/126)	0.73 (0.5–1.0)	5.8
Deep WM						
LLD/controls	11 (514/527)	1.92 (1.2–3.0)**	21.7*	13 (559/370)	0.39 (0.2–0.6)	26.1*
LOD/controls	7 (212/338)	2.64 (1.3–5.5)*	14.0*	5 (198/143)	0.46 (0.2–0.7)	2.5
LOD/EOD	9 (362/160)	4.33 (2.7–6.9)***	8.3	7 (165/134)	0.87 (0.6–1.1)	7.0
Combined WM						
LLD/controls				12 (598/490)	0.36 (0.2–0.5)	19.9*
LOD/controls				6 (258/308)	0.44 (0.3–0.6)	5.1
LOD/EOD				8 (262/183)	0.73 (0.5–0.9)	5.8

*p<0.05; **p<0.01; ***p<0.001.
EOD, early onset depression; LLD, late life depression; LOD, late onset depression; n, number of studies, $Q\chi^2$, Cochrane Q for non-combinability of odds ratios; Qd, "non-combinability" for d+ test; WM, white matter; WMH, white matter hyperintensities.

white matter comparisons. All studies comparing controls and LLD and those comparing LOD and controls for periventricular changes had significantly raised variability. To explore the effect of age differences between groups on differences in severity of WMHs, effect sizes were plotted against mean age differences between diagnostic groups for each study and, if appropriate, correlations were computed. Correlations were found for combined WMHs across LLD and controls and the age differences in these studies ($r = 0.61$, $df = 10$, $p = 0.46$; see appendix online), but there was no correlation in particular between effect sizes of studies comparing LOD and EOD and the age differences between these two groups in these studies.

WMH severity (binary analysis: absent or minimal versus moderate to large changes)

A χ^2 analysis with 2 degrees of freedom found a statistically significant association between diagnosis and severity for comparisons between (1) patients with LLD and controls (PVWMH, $\chi^2_{(2)} = 23.8$, $p<0.001$; DWM, $\chi^2_{(2)} = 24.8$, $p<0.001$), (2) patients with LOD and controls (PVWMH, $\chi^2_{(2)} = 18.5$, $p<0.001$; DWM, $\chi^2_{(2)} = 20.6$, $p<0.001$) and (3) patients with LOD and EOD (PVWMH, $\chi^2_{(2)} = 25.6$, $p<0.001$; DWM, $\chi^2_{(2)} = 22.1$, $p<0.001$). For all of these analyses, the proportion of patients with LLD/LOD appeared to increase with increased WMH severity.

DISCUSSION

Consistent with our hypotheses, our results indicate that WMHs are more common and severe in individuals with geriatric depression than in healthy controls, and specifically in individuals with late onset illness. Hitherto, small sample sizes and systematic differences in subject populations between studies, in imaging protocols and measurement techniques, have made comparison of results difficult and have prevented firm conclusions.[21] Combining all currently available data enables us to place greater confidence in what has previously been a conclusion from small scale partly under powered studies.

Interestingly, when late and early onset depression were compared, the odds of finding either deep or periventricular white matter changes were about 4.5. Similarly, the severity of WMHs was greater in LOD than in EOD patients. Our results therefore support the notion that LOD is aetiologically different from EOD, beyond previously observed neuropsychological differences.[25] Our results are consistent with age related subcortical neuropathological changes in LOD rather than genetic load and traumatic changes early in life which play an important role in the onset and course of EOD.[5–8] Reassuringly, the variability between studies comparing EOD and LOD is not greater than expected by chance; no confounders affecting studies in a different fashion are required to explain the observed variability. This may be due to the relatively homogeneous recruitment of depressed patients who only differ in age of onset but are likely to come from similar clinical patient populations. If comparisons are made between patients and controls, the observed greater variability between studies possibly results from differential recruitment of the control groups. Ideally, healthy volunteers should be randomly selected from a putative "normal population". In fact, they tend to be self selected, representing motivated, possibly more educated (if no monetary incentive is offered) or poorer (if the motivation is primarily financial) subjects. The screening process applied clearly determines to what extent controls are "super-normals", representative of their population or may suffer from unrelated illnesses. One method of recruiting controls has unfortunately been the relabelling of subjects as "normal" who were referred for a clinical scan, if no scan abnormality was found. Such groups of "ex-patients" may suffer from headaches, migraine, subjective cognitive impairment or other neurological or psychiatric symptoms.[13 20 50] Finally, healthy volunteers tend to be younger than patients with an age related illness, so the age difference between patient and control groups may play a significant role, as we found for the comparison of late life depression and controls with combined WMHs.

Our findings suggest that studies including patients with early *and* late onset will underestimate the true magnitude of differences in terms of both frequency and severity of WMHs. It is possible that negative studies include a high proportion of individuals suffering from EOD which may obscure important abnormalities of the individuals with LOD. It is therefore crucial to recruit a more homogeneous group of patients or to analyse EOD and LOD data separately in future studies of white matter changes.

Mechanisms of link between WMHs and depression

To date, the specific link between WMHs and the development of depression remains elusive. Here, we have shown that both

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MRI studies point to white matter changes in the brains of patients with LLD. On further examination, these appear to be located in the frontal and to a lesser degree the temporal cortex. Our results are therefore consistent with the vascular depression hypothesis,[23] which holds that white matter lesions are caused by cerebrovascular disease disrupting fibre tracts within frontostriatal circuits.[24] Because of their involvement in the regulation of mood,[21 51] disruption of frontostriatal circuits may lead to a disconnection syndrome[52] that corresponds to the clinical and neuropsychological profile of LLD.

However, most studies are of a cross sectional nature, making it difficult to show that hyperintensities do, in fact, cause geriatric depression. In order to directly test this hypothesis and to shed light on the progression and predictive value of hyperintensities in depression, longitudinal studies are needed.[12] In addition, research is needed to investigate if controlling cerebrovascular risk factors may slow the progression of WMHs and thereby decrease the incidence of geriatric depression.

Our findings do not agree with the alternative account that antidepressant treatment may cause the development of WMHs via cerebrovascular side effects and recurring episodes of subclinical cerebral ischaemia.[10 21] By definition, patients with EOD have been treated for a longer period of depression throughout their lives, so that they will have received a greater lifetime dose of antidepressant medications than patients with LOD. It follows that patients with EOD should show more severe WMHs than individuals with LOD. Our findings indicate that this is not the case. Longitudinal studies are required to document white matter changes over time and to investigate how these are related to the type and intensity of medication.[53]

Limitations of the data

Not all individual studies included in our analysis demonstrated a significant difference between patients with LOD/LLD compared with EOD or controls. This lack of significant difference has led some investigators to hypothesise that LOD does not represent a clinical entity that is pathologically distinct from EOD.[1 41] However, apart from lacking statistical power, a number of alternative explanations for negative results are possible.

Firstly, it has been suggested that it is not the overall volume of white matter lesions but instead their specific location[54–56] that plays an important role in the onset and development of geriatric depression. Consistent with this, several studies have observed a strong association between WMHs occurring in the orbitofrontal cortex and presence of LLD.[53 54 56–58] However, the majority of studies of LLD employ rating scales that fail to incorporate lesion lateralisation or site. Increased efforts to take into account lesion lateralisation relative to the occurrence of depression may therefore result in more consistent results and could play an important role in delineating the neuroanatomical substrates of LLD.[54]

Secondly, there is disagreement as to what constitutes a valid age cut-off that can be used to dichotomise subjects into early versus late onset groups.[1] As a result, studies included in this review differed in how they defined LOD, and participants classified as LOD in one study may have been classified as EOD in another study. In addition, inaccurate medical records or reporting bias[40 59] may have further complicated the classification of participants and thereby obscured or enhanced differences between study groups. The concept of LOD suffers from another definitional problem. Individuals with EOD may have been ill early in life and then have recovered, such that they may not necessarily have a longer duration of illness than patients with LOD. We cannot be certain that studies included in this review controlled for this.

Thirdly, studies included in this review are characterised by substantial variation with respect to the rating scales employed to assess WMH. While the majority of studies used visual rating scales, some authors have begun to use a more objective semiautomated segmentation technique to measure WMH lesion volumes.[1 14 60] It has been argued that quantitative ratings of WMH allow for much more precise measurement of hyperintensities and should thereby facilitate detection of small, but significant, differences between groups[60] that may have gone unnoticed in studies purely relying on visual rating scales. Moreover, there is disagreement regarding which hyperintense signals seen on MRI scans should be considered pathological and how they should be graded.[61] This may readily contribute to inconsistent results. Finally, factors relating to imaging protocol (eg, field strength of magnet, number, thickness, contiguity and orientation of slices) add to the heterogeneity of studies included in this review and thereby to the heterogeneity of individual findings. In order to facilitate measurement of progression of hyperintensities, future studies should employ longitudinal designs together with standardised treatment protocols and quantitative measurement of WMHs.[60] Similar considerations apply to the new techniques of measuring FA and quantitative tractography.

CONCLUSION AND CLINICAL IMPLICATIONS

Geriatric depression is a heterogeneous condition characterised by diverse aetiologies, including biological, genetic, social and psychological factors.[27] Here, we systematically review published MRI studies in order to elucidate whether WMHs may be one of the factors associated with the onset and development of depression in old age. Our findings indicate that in individuals with LOD and LLD in general, WMHs are more common and also more severe than in healthy controls. Our findings also support the notion that individuals with LOD are different from individuals with EOD and raise the question of whether this patient group should be considered a separate clinical entity. Although the exact mechanisms are unclear, it would appear that WMHs play a vital role in the onset and development of LOD. Longitudinal studies are needed in order to clarify the mechanism underlying the link between hyperintensities and geriatric depression. This is an exciting avenue for future research, particularly when employing advanced imaging techniques, such as diffusion tensor imaging[52 62–66] which is superior at assessing white matter integrity and detecting sites where hyperintensities may directly predispose to the development of depression.[18 53] Delineation of the underlying mechanisms may have an impact on how we approach prevention and treatment of LOD and may lead to novel strategies aimed at managing geriatric depression.[6]

Finally, our findings demonstrate that future studies should reduce heterogeneity by examining LOD and EOD separately. Failure to do so may lead to underestimation of the presence and severity of brain abnormalities in relation to healthy controls and may obscure important indicators of the aetiology of LOD.

Funding: We acknowledge the financial support of the Gordon Small Charitable Trust.

Competing interests: None.

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J Neurol Neurosurg Psychiatry 2008 79: 619-624 originally published online August 23, 2007
doi: 10.1136/jnnp.2007.124651

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