Published in final edited form as:

Am J Geriatr Psychiatry. 2016 January ; 24(1): 42–49. doi:10.1016/j.jagp.2015.03.001.

Late-life Depression Modifies the Association between Cerebral White Matter Hyperintensities and Functional Decline among Older Adults

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Abstract

Objective—Vascular lesions seen through brain imaging as hyperintensities are associated with both depression and functional impairment in older adults. Our objective was to determine if the relationship between the volume of cerebral white matter hyperintensities (WMH) and functional decline differed in the presence of late life depression.

Design—Secondary analysis of data collected through the Neurocognitive Outcomes of Depression (NCODE) Study. Analysis techniques included general linear mixed models examining trajectories of functional change predicted by lesion volume at baseline.

Participants—381 participants (244 patients diagnosed with major depression and 137 never depressed comparison participants) ages 60 years and older followed for up to 16 years.

Measurements—WMH volume was measured through analysis of brain MRI data. Functional limitations included difficulties with basic activities of daily living (ADL) tasks, instrumental tasks (IADLs), and mobility.

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Conflict of Interest: No Disclosures to Report

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Results—Those participants who were both depressed and had a higher volume of WMHs at baseline were most at risk for functional decline across all measures of function. Among the never depressed, those with a higher WMH volume at baseline had a more accelerated rate of functional decline than those with lower WMH volume, while those who were depressed with lower volume of WMH started with more limitations than the never depressed but appeared to progress at a rate similar to those who were never depressed with lower WMH.

Conclusions—Older patients with both cerebrovascular risk factors and depression are at an increased risk for functional decline, and may benefit from the treatment of both conditions.

Keywords

Depression; functional impairment; lesions; white matter hyperintensities; longitudinal

Late life depression is associated with a number of negative medical and psychological outcomes, due, in part, to a course that is often chronic and recurring (1). One such negative consequence of depression is a decline in functional status. While the associations between depression and functional impairment have been well documented, the pathways are complex, as both conditions can be a cause, consequence, or comorbidity of the other (1–3). Depression is one of the leading causes of disability, yet the components and correlates of the depression experience which impact functional decline are still under study.

Increased volume of cerebral white matter hyperintensities (WMH), as observed through brain imaging, has been linked to both late life depression and functional impairment. Specifically, “vascular depression” has been proposed as a subtype of late life depression, particularly among those with a late onset, which exhibits increased severity of hyperintensities in both subcortical gray and white matter (4–6). In addition to a later onset, increased WMH volume has been linked to poorer outcomes in geriatric depression (7). Much research has focused on cognitive decline associated with increased WMH volume, particularly among older depressives (8–11). WMH volume has also been associated with functional limitations (12, 13), impaired mobility (14), gait and motor disturbances, falls, and poor balance (15–17) in community studies of older adults. In longitudinal studies, increased WMH volume predicted incident falls and increased functional impairment, decreased mobility, and becoming frail (13, 18–22). Increased WMH volume has also been shown to predict becoming dependent due to motor and cognitive deterioration (23).

That vascular changes in the brain are associated with both functional decline and late life depression raises the possibility that depression and disability may share a common risk factor in vascular lesions. A second hypothesis is that depression modifies the relationship between WMH and functional status (1). It is not fully established whether increased WMH volume predicts functional decline within the context of late life depression or whether depression modifies the relationship between WMH volume and functional decline.

The purpose of the analyses presented here was to determine if the longitudinal association between WMH and functional decline differed in the presence of late life depression. We hypothesized that greater WMH volume at baseline would predict an increase in functional

limitations over time, and that the effect of WMH volume would be greater among patients with late life depression compared to those never depressed.

Methods

Study Sample

The study sample was 381 participants ages 60 years and older, including 244 patients who met DSM criteria for major depression and 137 never depressed comparison participants who were enrolled in the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study at Duke University. The study has been described elsewhere (8). In summary, NCODE is a guideline-based prospective naturalistic treatment study of older patients with major depression currently in its 19th year. The sample includes both incident and recurrent cases of depression recruited from psychiatry and primary care clinics. Patients and comparison participants had to be free of dementia or suspected cognitive impairment at the time of enrollment. Other exclusion criteria included a diagnosis of another major psychiatric condition; any primary neurological illness; active alcohol abuse or dependence; or metal in the body which could interfere with brain magnetic resonance imaging. Comparison participants were recruited from the Duke Center for Aging subject registry. Participants in this analysis have been followed for up to 16 years. All participants provided written consent at the time of enrollment. The research protocol was reviewed and approved annually by the Duke University Institutional Review Board.

Study Measures

Participants were administered the Duke Depression Evaluation Schedule (DDES) (24) at enrollment and annually thereafter. This composite questionnaire includes the Center for Epidemiologic Studies – Depression (CES-D) scale (25) to screen for depression in addition to questions about health and functioning. All potential cases of depression were confirmed by a geriatric psychiatrist for entry into the patient group. The DDES also included sections of the Diagnostic Interview Schedule (DIS) (26). The DIS was used to document a lack of history of major depression in the comparison group.

The number of functional limitations was determined based on responses to 16 items in the DDES that measured limitations in basic activities of daily living (ADLs), instrumental ADLs and mobility. Basic ADL tasks included seven items modified from Katz et al (27): eating, dressing, grooming, walking, bathing, using the toilet, and bending to pick up objects off the floor. IADL tasks included six items modified from Fillenbaum et al (28): getting around in the neighborhood, shopping for groceries or household items, preparing meals, cleaning house, doing yard work or gardening, and keeping track of money and bills. Mobility tasks included three items modified from Rosow and Breslau (29): walking one-fourth of a mile, walking up and down one flight of stairs, and taking care of or watching children. For each task, participants were asked “Can you...” and responses were coded as yes without difficulty, yes but with difficulty, or unable to do. For these analyses, each task was coded as 0=no difficulty and 1=some difficulty or unable to do. The responses were then summed to reflect the total number of limitations across the three domains (range 0–16).

Several control variables were included at their baseline value. Sociodemographic variables included age, sex, race (white vs. non-white), and years of education. Cognitive status was based on the total score from the Mini Mental State examination (MMSE) (30). Self-reported high blood pressure was coded in response to the question “Do you have high blood pressure or hypertension?”

The total volume of WMHs (periventricular and deep white) at baseline enrollment was the key independent variable of interest. The imaging acquisition protocol has been previously described (31). In summary, participants were imaged with a 1.5 Tesla whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI) using the standard head (volumetric) radiofrequency coil. A dual-echo fast spin-echo acquisition was used for the volumetric measurements of WMH. The images were processed by analysts blinded to all identifying information including depression diagnosis and functional status. Once the brain was segmented using a semi-automated technique, the lesions were manually identified from among the lesion-intense regions on the segmentation. The measure of total WMH volume was log transformed because of a skewed distribution in its original form.

Analysis Procedures

We compared the baseline characteristics of the depressed patients to the never depressed comparison participants using t-statistics for continuous variables and chi-square statistics for categorical variables. We estimated linear mixed models to measure the associations between white matter lesion volume at baseline and change in functional status over time for each participant, controlling for age, sex, race, years of education, MMSE score, and self-reported hypertension at the time of study enrollment. Time was measured in years since baseline enrollment (range 0–16).

To address our primary hypothesis, we estimated whether the average trajectory of functional change predicted by white matter lesion volume varied by depression status using an interaction term, WMH volume*depression status. To estimate whether the effects of depression status and WMH volume as well as their interaction varied over time we included higher order terms, WMH volume*depression status*time. Finally, to assess if the effect of time was linear, we included higher order terms for time in the model.

While estimating the number of functional limitations traditionally suggests the use of a generalized linear regression model, we chose to use a general linear model to be able to examine interaction on an additive scale. Specifically, relevant theoretical (32) and methodological (33) work indicates these modifying effects should be estimated on an additive scale (effects on a rate or count) rather than on a multiplicative scale (effects expressed as rate ratios) which would be done in a generalized model. From several available models, we chose the simplest model to examine patterns of change over time, a general linear mixed model, to estimate the interaction or effect modification. To address misspecification of the distribution of the dependent variable (number/count of functional limitations) and the impact of influential observations on the estimates, for each mixed model we employed bootstrapping of participants (n=500 iterations/models). We report the mean regression coefficient from the 500 models, the adjusted standard deviation of the parameters, and the significance level for each parameter in the model. Standard deviations

were calculated controlling for both the estimated variance and the variance of the bootstrap (34, 35). All analyses were conducted using SAS software (Version 9.3; SAS Institute, 2011).

Results

The sample characteristics are shown in Table 1. Overall, the sample was predominantly White, female, and well-educated. Patients had on average fewer years of education and were more likely to report high blood pressure relative to the never depressed. Patients had significantly lower MMSE scores on average than the comparison group but the difference in the means was not clinically meaningful. At the time of baseline enrollment, the patients as a group had more functional limitations. These differences were observed across ADL tasks, IADL tasks, and mobility as well as the total number of limitations. Patients had higher volumes of WMH at baseline. The median length of follow-up was five years. Depressed patients were followed on average for 5.5 (4.7) years, while the never depressed were followed for 6.9 (4.4) years ($T[379]=2.71$, $p=0.0070$).

Prior to the bootstrap models, we assessed whether the effects of WMH, depression group, and their interaction over time were linear by including four higher order terms in the models to represent time squared: time*time, time*time*WMH, time*time*depression group, and time*time*WMH*depression group. The significance of the nonlinear effects of time was assessed through an omnibus test of these four higher order terms. This omnibus log likelihood ratio test with 4 degrees of freedom was significant for the total number of limitations ($\chi^2=66.6$; $p<0.0001$) and for IADL ($\chi^2=43.4$; $p<0.0001$) and ADL limitations ($\chi^2=37.9$; $p<0.0001$), but not significant for mobility. For consistency, we left the four higher order terms for time in all of the models.

Table 2 shows the results of the random effects mixed model with the total number of functional limitations as the dependent variable. Controlling for age, race, sex, years of education, self-reported hypertension and MMSE score at their baseline value, the effect of WMH volume at baseline on the change in functional status over up to 16 years of follow-up differed by depression status over time. Women were at an increased risk for functional decline, as were those with fewer years of education and lower cognitive scores.

In Figure 1, we show the predicted change in the total number of functional limitations over time by depression status based on the mean regression coefficients from the bootstrapped models and by two levels of WMH volume. For purposes of the graphing, we defined low WMH volume and high WMH volume as the values found at the 25 and 75 percentiles of the distribution respectively. Those participants who were both depressed and had a higher volume of WMH at baseline were most at risk for functional decline. Among the never depressed, those with a higher WMH volume at baseline had a more accelerated rate of functional decline, while those who were depressed with lower volume of WMH started with more limitations but appeared to progress at a rate similar to those who were never depressed with lower WMH.

While our intent was to assess the possible modifying effect of depression on an additive scale, we estimated two additional models that assessed this modification on a multiplicative scale. We first estimated a mixed model where the dependent variable was the log of the total count of functional limitations. We next estimated a generalized marginal means model where the dependent variable was the count of limitations using a negative binomial distribution to adjust for overdispersion. While these models are not on a comparable scale to the one we present in this manuscript, we obtained essentially similar conclusions about the significance of this modifying effect.

We conducted exploratory analyses to see if the modifying effect of depression was evident across the three domains of function – basic ADLs, IADLs, and mobility. The effect modification was strongest for trajectories of IADL function, in a similar pattern to that observed for total number of limitations. As shown in Figure 2, the same pattern was evident across all domains of function although for ADL the differences by depression status were less robust.

As a final check to be sure the moderating effect of depression was not due to depressed patients with higher volumes of WMH progressing to dementia, we excluded 36 participants whose last MMSE score was less than 25. The results were essentially unchanged across all domains of function.

Conclusions

To our knowledge, this is the first study to examine differences in the longitudinal effects of cerebral WMH on functional decline comparing those with late life depression to never depressed older adults. We report new findings that depression is a modifier in the association between WMH and functional decline in older adults, which suggests one pathway by which older depressed adults develop disability. Those older adults with increased WMH volume who were also depressed had a sharper increase in the number of limitations over time compared to older adults with a lower volume of WMH who were also depressed and to older adults without a history of depression. That depression is a moderator in the association between white matter pathology and functional decline suggests a unique contribution of depression. This contribution appears to be generally consistent across different domains of function.

These findings extend those reported earlier from cross-sectional analyses that the association between WMH and level of functional status differed in the presence of depression (36, 37). We recently reported that increased WMH volume was significantly associated with more functional limitations among older patients with depression but was not associated among older adults without a history of depression (36). These findings were from the NCODE sample but examined these associations only at the time of study enrollment. Using cross-sectional analyses from the nationally representative NIMH Collaborative Psychiatric Epidemiology Surveys (CPES), Gonzalez et al. reported among adults age 50 years and older with a lifetime diagnosis of major depression that 22.1% were considered to have the vascular depression subtype. Vascular depression subtype was

associated with increased functional impairment relative to the nondepressed population and relative to older adults meeting criteria for major depression alone (38).

Our significant longitudinal findings may also be due in part to changes in cognition over the follow-up period. Depressed patients with more WMH (10) and greater change in WMH over time (8) are more likely to experience incident dementia, which is a risk factor for functional decline (39). It is also possible that the presence of both late life depression and cerebral WMH associated with functional status, including gait and balance, represents more significant global cerebrovascular disease.

Our research has several limitations. Functional status was measured through self-report and the perception of functional status could have been influenced by depression. Future research could include physical performance measures rather than relying on self-report. We did not control for the severity of the depression at the time of the index episode or at the start of the index episode or for changes in depression status and cognition over time which may have affected functional status. Attrition rates, generally due to dropping out of the study, were higher for the depressed patients compared to the never depressed and greater for those with higher volumes of WMH. We did not have data on lesion location which prevented us from a closer examination of these differences by depression status; that is, whether some lesions were associated with depression while others were associated with physical function. Some researchers have suggested that lesion subtyping by location, however, may be of limited value since regional measures are highly correlated with total burden (40). Our comparison group was, as a group, generally healthy, and participants in both groups were able to come to the clinic for the follow-up assessments. That is, persons with high functional limitations likely did not enroll in the study, and increased limitations may have caused participants to drop out of the study. Finally, baseline in this study refers to the time of study enrollment and for depressed patients, the time of the index episode. Baseline does not refer to a sentinel depression/WMH event from which trajectories of time can be assessed and compared. While we cannot rule out the possibility of a Type 1 error, the bootstrapped models reduce this possibility (34).

The strengths of the study are clear. The data derive from a large clinical sample of depressed older adults and never depressed comparison participants followed for up to sixteen years. NCODE is the largest longitudinal study conducted to date following patients with a diagnosis of depression, and focuses on patients with major depression rather than depressive symptoms. Using the WMH assessments in combination with multiple years of follow-up is particularly informative as functional decline can be a gradual process. We used a highly reliable quantification technique for WMHs (31). We also applied rigorous statistical techniques in the form of mixed models that can model correlated changes over time and allow for both differences within individuals over time as well as between person differences. Future research will examine the impact of WMH volume on specific tasks or groups of items on the functional status measures. For example, some of the IADL tasks such as paying bills and shopping are dependent on intact cognition.

Given the projected increases in the number of older adults over the next several decades, identifying factors that increase the risk of and protect against functional decline is of much

clinical and public health importance. Depression is a common and potentially modifiable risk factor. Interventions to prevent the worsening of lesion burden among older adults with cerebrovascular risk factors who are also depressed through strict management of conditions including hypertension and diabetes may prevent further or incident functional decline.

Acknowledgments

This research was supported by NIMH grants R03 MH 095917, R01 MH54846, and K24 MH70027, the Duke University BIRCWH (K12 HD043446), and the Duke Claude A. Pepper Center (2P30 AG028716-08). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Figure 1.

Figure 2.

Table 1

Characteristics of the Sample at Enrollment

Characteristic	Total Sample (n=381)	Depressed Patients (n=244)	Never Depressed Comparison Group (n=137)	Significance
No. Female (%)	262 (68.8)	166 (68.0)	96 (70.1)	$\chi^2[1]=0.17$, $p=0.6801$
No. White (%)	318 (83.5)	209 (85.7)	109 (79.6)	$\chi^2[1]=2.36$, $p=0.1244$
Mean Age (sd)	70.1 (6.9)	69.7 (7.3)	70.7 (6.1)	$T[325.2]=1.40$, $p=0.1622$
Mean Yrs of Education (sd)	14.3 (2.7)	13.7 (2.9)	15.3 (2.0)	$T[364.7]=6.68$, $p<0.0001$
Mean MMSE Score (sd)	28.4 (2.2)	28.0 (2.5)	28.9 (1.2)	$T[367.3]=4.75$, $p<0.0001$
No. with High Blood Pressure (%)	137 (36.0)	101 (41.4)	36 (26.3)	$\chi^2[1]=8.71$, $p=0.0032$
Mean No. ADL Limitations (sd)	0.4 (1.2)	0.6 (1.4)	0.0 (0.0)	$T[243]=-6.43$, $p<0.0001$
Mean No. IADL Limitations (sd)	1.3 (1.9)	2.0 (2.1)	0.1 (0.4)	$T[269.4]=-13.71$, $p<0.0001$
Mean No. Mobility Limitations (sd)	0.6 (1.0)	0.9 (1.2)	0.1 (0.4)	$T[339.7]=-9.48$, $p<0.0001$
Mean No. Total Limitations (sd)	2.3 (3.7)	3.5 (4.1)	0.2 (0.6)	$T[262.1]=-12.17$, $p<0.0001$
Mean No. (log) Total White Matter Lesions (sd)	1.66 (0.7)	1.73 (0.7)	1.54 (0.6)	$T[321.8]=-2.64$, $p=0.0087$

Table 2

The association between (log) cerebral white matter hyperintensities and the change in number of functional limitations over time (n=381)

	Mean Parameter Estimate	Adjusted Standard Deviation	Significance
Intercept	8.03	4.13	Z=1.95, p=0.0523
Time in Years	0.08	0.19	Z=0.41, p=0.6784
(Log) WMH	-0.25	0.43	Z=-0.58, p=0.5597
Depressed Group	0.50	0.91	Z=0.54, p=0.5873
Age in Years	0.05	0.03	Z=1.52, p=0.1290
Female	1.06	0.33	Z=3.16, p=0.0017
White	-0.48	0.47	Z=-1.04, p=0.3000
Years of Education	-0.15	0.08	Z=-1.98, p=0.0482
Hypertension	0.12	0.38	Z=0.31, p=0.7546
MMSE Score	-0.30	0.11	Z=-2.73, p=0.0067
Depression Group*WMH	1.09	0.54	Z=2.03, p=0.0432
WMH*Time	0.02	0.13	Z=0.13, p=0.8992
Depression Group*Time	0.07	0.28	Z=0.26, p=0.7937
Depression Group*WMH*Time	-0.26	0.19	Z=-1.37, p=0.1715
Time*Time	-0.01	0.02	Z=-0.44, p=0.6582
Time*Time*WMH	0.01	0.02	Z=0.50, p=0.6202
Time*Time*Depression Group	-0.03	0.03	Z=-1.04, p=0.2966
Time*Time*Depression Group*WMH	0.04	0.02	Z=1.75, p=0.0812