Depression Plays a Moderating Role in the Cognitive Decline Associated With Changes of Brain White Matter Hyperintensities

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ABSTRACT

Objective: In the elderly, depression and white matter hyperintensities (WMH) are common and associated with cognitive impairment. This study investigated the possible interactions between depression and WMH in their influences on cognition of the elderly.

Methods: Using multiple neuropsychological tests, we evaluated the cognitive function of 122 community-dwelling elders with depression at baseline between November 2008 and February 2009. Major depressive disorder, dysthymic disorder, and minor depressive disorder were diagnosed according to *DSM-IV* criteria. Subsyndromal depressive disorder was operationally defined using a modification of *DSM-IV* criteria. We visually rated WMH severity according to the modified Fazekas scale and calculated WMH volume using an automated method. We defined WMH (+) as having a score of 2 or higher on the modified Fazekas scale. In the 3-year follow-up study, baseline participants were reassessed between November 2011 and February 2013 with the same methodology.

Results: Baseline depression was associated with a decline over 3 years in the Categorical Verbal Fluency Test (VFT) ($P = .001$), Word List Memory Test (WLMT) ($P = .019$), Trail Making Test A (TMT-A) ($P = .018$), and Mini-Mental State Examination (MMSE) ($P = .017$), while baseline WMH (+) was associated with a decline in WLMT ($P = .039$) only. An increase of WMH volume over 3 years was associated with a decline in the performances of VFT ($P = .044$), WLMT ($P = .044$), Word List Recall Test ($P = .040$), Word List Recognition Test ($P = .036$), and TMT-A ($P = .001$) over the same period only in the subjects with depression at baseline.

Conclusions: Depressive disorder and WMH are interactively associated with the poor performance of multiple cognitive functions. Depressive disorder may moderate the cognitive decline associated with the changes of brain WMH.

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White matter hyperintensities (WMH) are common in the elderly with a prevalence ranging from 50% to 98%.[1–3] WMH have been shown to progress with aging, and they are associated with both depression[4–8] and cognitive impairment[9–11] in late life.

Depression in late life has also been frequently associated with cognitive impairment.[12,13] Studies have found that approximately two-thirds of patients with late-life depression show cognitive impairment,[14,15] and many of them exhibit residual cognitive impairment even after remission of depression by successful antidepressant treatment.[14,16,17] Furthermore, depression has been considered a risk factor for developing dementia.[18,19] One study[20] found that each depressive episode in the elderly was associated with a 14% increased risk for all-cause dementia during a median follow-up period of 24.7 years, suggesting that the impact of depression on cognition may be cumulative.

Recently, we found that the severity and outcome of late-life depression was strongly associated with the presence of WMH. In a randomly sampled community-dwelling elderly population, more than half of the patients with major depressive disorder (MDD) had magnetic resonance imaging (MRI) evidence of moderate to severe levels of WMH.[21] Greater WMH volume was an independent predictor for depressive disorder after 3 years,[21] and depressive patients with greater increase of WMH over time were less likely to be remitted.[22,23] Krishnan and colleagues defined this condition as "vascular depression."[5,24,25]

In this prospective study of community-dwelling elderly individuals, we compared the baseline cognitive function of the participants by the presence of depressive disorder and WMH, and we investigated the impacts of the changes in depressive

Clinical Points

- Depression disorder and white matter hyperintensities (WMH) are interactively associated with the poor performance of multiple cognitive functions. Depressive disorder may play a moderating role in the influences of WMH on cognitive functions.
- As depression and WMH are common and coexist frequently in the elderly, the prevention of depression and WMH is one of best strategies to maintain cognitive function in the elderly.

symptoms and WMH volumes on the magnitude of cognitive decline in subjects with and without depressive disorder at baseline.

METHODS

Subjects

This study was conducted as a part of a longitudinal community-based study[21] on the epidemiology of MRI-defined vascular depression. The design of the study population is described in detail elsewhere.[26] Among the residents of Yong-in, Korea, 1,060 who were aged 65 years or older were randomly sampled, and 783 of them completed the baseline assessment. Subjects were asked to participate in the study via letters and telephone calls. All participating subjects were fully informed of the study protocol and were provided written statements of informed consent that were signed by them or their legal guardians. The Institutional Review Board of Seoul National University Hospital, Korea, approved this study protocol.

Study Design

The baseline study was conducted in 2 phases between November 2008 and February 2009. In the phase 1 population survey, the Korean short version of Geriatric Depression Scale (SGDS)[27,28] was given to all survey participants (N = 783). Participants who responded to the phase 1 survey were classified into 2 groups according to their SGDS scores: a higher risk group for depression (SGDS-K score ≥ 8; n = 166; 21.2%) and a lower risk group for depression (SGDS-K score < 8; n = 617; 78.8%). All subjects from the higher risk group and 10% of the subjects who were randomly sampled from the lower risk group were invited to the phase 2 clinical evaluation (n = 228). Among them, 122 subjects consisting of 42 from the lower risk group for depression and 80 from the higher risk group completed the phase 2 evaluation (response rate = 53.5%; see Supplementary Figure 1). All phase 2 respondents completed the Korean version of the Mini-International Neuropsychiatric Interview (MINI)[29] administered by a neuropsychiatrist to diagnose depressive disorders. Standardized clinical interviews and neurologic and physical examinations were also conducted using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) clinical assessment battery (CERAD-K).[30] The Neuropsychological Assessment Battery (CERAD-K-N)[30] and Frontal Assessment Battery (FAB)[31] were administered by neuropsychologists or trained research nurses. Participants of phase 2 evaluation also completed 3.0 Tesla brain MRI (Philips Medical Systems, Eindhoven, The Netherlands).

The 3-year follow-up study was conducted between November 2011 and February 2013. We contacted 122 subjects who had engaged in phase 2 of the baseline study and excluded 21 subjects who had newly developed serious illnesses contributing to cognitive dysfunction during the 3-year follow-up period or could not undergo MRI. Among a sample of 101 subjects, 54 subjects consisting of 23 from the baseline lower risk group for depression and 31 from the higher risk group participated at the 3-year follow-up and completed the same assessments as in phase 2 of the baseline study (see Supplementary Figure 1).

Clinical Assessments

The presence of depressive disorder was defined as having any disorder including MDD, dysthymic disorder (DD), minor depressive disorder (MnDD), and subsyndromal depressive disorder (SSD). MDD and DD were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), criteria, and MnDD according to the research criteria in *DSM-IV* Appendix B. SSD was operationally defined as having 5 or more current depressive symptoms with core depressive symptoms such as depressive mood or loss of interest or pleasure with reduced time thresholds of "more than half a day" instead of "most of the day" and "more than 7 days" instead of "nearly every day" over a 2-week period.

Among the CERAD-K-N, the following neuropsychological tests were administered to subjects: Categorical Verbal Fluency Test (VFT), 15-item Boston Naming Test (sBNT), Korean version of the Mini-Mental State Examination (MMSE), Word List Memory Test (WLMT), Word List Recall Test (WLRT), Word List Recognition Test (WLRcT), and Trail Making Test A (TMT-A). All instruments were validated in the Korean population. Dementia, stroke, and other serious medical, psychiatric, and neurologic disorders that could affect mental function were excluded from this study. All subjects possessed adequate vision and hearing, although many wore glasses and some required hearing aids.

MRI Acquisition and Processing

Participants underwent fluid-attenuated inversion recovery (FLAIR) MRI using the following protocol: repetition time = 9,900 ms; echo time = 160 ms; inversion time = 2,500 ms; number of excitations = 1; flip angle = 90°; field of view = 240 mm; axial plane matrix = 256 × 256 mm; thickness = 3 mm; no interslice gap; slice number > 40. All study procedures were implemented using custom written codes running in MATLAB 2010a (MathWorks, Natick, Massachusetts), and functions from Statistical Parametric Mapping software (version SPM8; Wellcome Trust Centre

Table 1. Comparison of Clinical Characteristics of Subjects Defined by Depressive Disorder and White Matter Hyperintensities

	Subjects With Depressive Disorder at Baseline (n = 63)				Subjects Without Depressive Disorder at Baseline (n = 59)				
Characteristic	All Subjects	WMH (+)	WMH (–)	*P* Value[a]	All Subjects	WMH (+)	WMH (–)	*P* Value[a]	*P* Value[b]
Number	63	25	38	…	59	22	37	…	.786
Age, y, mean ± SD	71.2 ± 5.1	74.1 ± 6.1	69.8 ± 3.6	.001	70.3 ± 4.7	72.6 ± 5.6	68.8 ± 3.3	.002	.156
Female, n (%)	46 (73.0)	19 (76.0)	27 (71.1)	.665	29 (49.2)	12 (54.5)	17 (45.9)	.523	.007
Education, y, mean ± SD	7.3 ± 5.5	6.6 ± 5.1	7.8 ± 5.9	.409	10.2 ± 5.8	7.8 ± 5.3	11.6 ± 5.6	.013	.006
MMSE score, mean ± SD	23.6 ± 4.4	22.2 ± 5.4	24.6 ± 3.3	.032	26.3 ± 3.5	25.6 ± 3.5	26.6 ± 3.5	.409	< .001
SGDS score, mean ± SD	11.3 ± 2.0	11.9 ± 2.2	11.0 ± 1.8	.070	4.3 ± 3.7	4.4 ± 3.2	4.2 ± 3.7	.878	< .001
Hypertension, n (%)	34 (54.0)	17 (68.0)	17 (44.7)	.070	32 (54.2)	15 (68.2)	17 (45.9)	.097	.976
Diabetes mellitus, n (%)	15 (23.8)	10 (40.0)	5 (13.2)	.014	11 (18.6)	3 (13.6)	8 (21.6)	.446	.486
Prior MDD, n (%)	15 (23.8)	4 (16.0)	11 (28.9)	.238	1 (1.7)	0	1 (2.7)	.437	< .001
WMH volume (mL)	12.6 ± 13.6	22.4 ± 17.2	6.2 ± 3.7	< .001	9.9 ± 8.1	17.5 ± 7.8	5.4 ± 3.8	< .001	.231

[a] *t* Test for continuous variables and χ^2 test for categorical variables between the WMH (+) and WMH (–) subjects stratified by the presence of depressive disorder.
[b] *t* Test for continuous variables and χ^2 test for categorical variables between the subjects with depressive disorder and those without depressive disorder.
Abbreviations: MDD = major depressive disorder, MMSE = Korean version of the Mini-Mental State Examination, SGDS = Korean version of the short-form Geriatric Depressive Scale, WMH = white matter hyperintensities, WMH (+) = WMH of grade ≥ 2 on the modified Fazekas scale in deep white matter or subcortical gray matter, WMH (–) = WMH of grade < 2 on the modified Fazekas scale.
Symbol: … = not applicable.

for Neuroimaging at University College London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm). WMH volumes were measured using a fully automated monospectral segmentation method for WMH using FLAIR MRIs; methods for this technique have been previously published.[32]

WMH were rated by the modified Fazekas scale,[33] a visual analog scale (see Supplementary Figure 2). Using this scale, WMH were dichotomously classified as WMH (+) with grades of 2 or 3 and WMH (–) with grades of 0 or 1. Patients were defined as having vascular depression if they suffered from any type of depressive disorder and had a score of 2 or more on the modified Fazekas scale for either deep WMH or subcortical gray matter ratings, namely WMH (+).[24,25,33,34] Final ratings of the modified Fazekas scale were determined by a panel of 4 neuropsychiatrists (J.H.P., S.B.L., J.J.L., and K.W.K.).

Statistical Analyses

All statistical analyses were performed using the SPSS version 15.0 statistical package (IBM Corp, Armonk, New York). Among the 4 groups defined by depressive disorder and WMH status at the baseline assessment (ie, those without both depressive disorder and WMH, with depressive disorder only, with WMH only, and with both depressive disorder and WMH), clinical characteristics and age-, sex-, and education-standardized scores were compared using analysis of variance (ANOVA) with Bonferroni post hoc comparison or χ^2 test. The differences between neurocognitive test scores at baseline and 3-year follow-up study were analyzed by mixed-model ANOVA. The associations of 3-year changes in SGDS score and WMH volume with 3-year changes in neurocognitive test scores were analyzed by a general linear model adjusting for age, sex, and education. For the volume of WMH, we used a logarithmic transformation to produce normally distributed data.

RESULTS

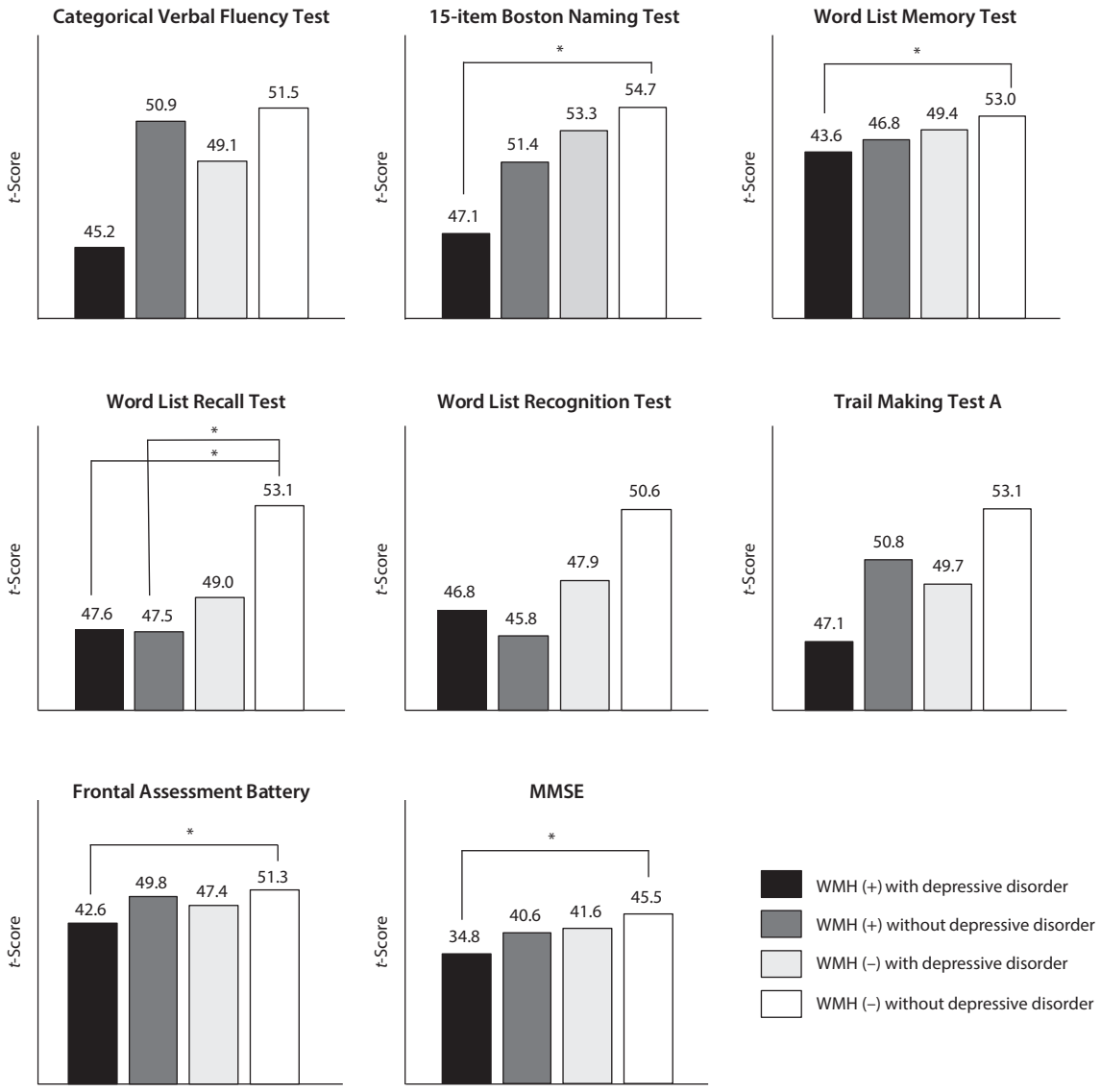
Demographical Characteristics

In the baseline study, 122 subjects with a mean ± SD age of 70 ± 4.9 years (women: 61.5%) were enrolled. Among them, 63 had depression (16 MDD, 3 MnDD, 2 DD, and 42 SSD) and 47 were WMH (+). Table 1 shows the clinical characteristics of the 4 groups categorized by the presence of depression and WMH. Among subjects with depression, 25 (39.7%) were WMH (+) while of subjects without depression, 22 (37.3%) were WMH (+) (χ^2 test, $P = .786$). The mean ages of the WMH (+) groups were higher than those of the WMH (–) groups in both depressed and nondepressed groups. Women were more highly represented in the depressed groups. The mean SGDS scores were not significantly different between the WMH (+)and WMH (–) groups in subjects with and without depression. Likewise, the frequencies of hypertension were not significantly different in both depressed and nondepressed groups. Among subjects with depressive disorder, diabetes was more frequent in WMH (+) subjects than in WMH (–) subjects. The frequencies of prior MDD were more prevalent in the depressed group than in the nondepressed group but were not significantly different between the WMH (+) and WMH (–) groups in subjects with and without depression.

Performances on Neurocognitive Tests Among the 4 Groups

WMH (+) subjects with depression (ie, those with vascular depression) exhibited the poorest performance on neurocognitive tests among the 4 groups (Figure 1). For the majority of tests, a statistically significant difference existed between WMH (+) subjects with depression and WMH (–) subjects without depression. This was observed for the sBNT, WLMT, WLRT, FAB, and MMSE scores. Additionally, when compared with WMH (–) subjects without depression, the

Figure 1. Comparison of Age-, Sex-, and Education-Standardized *t*-Scores of Neurocognitive Tests Between Groups Defined by Depressive Disorder[a] and White Matter Hyperintensities



[a]Having any major depressive disorder, minor depressive disorder, dysthymic disorder, or subsyndromal depressive disorder.
*$P < .05$, ANOVA with Bonferroni post hoc comparison.
Abbreviation: MMSE = Korean version of the Mini-Mental State Examination, WMH (+) = white matter hyperintensities of grade ≥ 2 on the modified Fazekas scale in deep white matter or subcortical gray matter, WMH (–) = WMH of grade < 2 on the modified Fazekas scale.

mean *t*-score of the WLRT was lower in WMH (+) subjects without depression.

Influence of Baseline Depressive Disorder and WMH on 3-Year Cognitive Changes

In mixed-model ANOVA, the baseline depressive disorder was associated with negative score changes in the VFT ($P = .001$), WLMT ($P = .019$), TMT-A ($P = .018$), and MMSE ($P = .017$), while baseline WMH (+) was associated with a negative score change in the WLMT ($P = .039$) (Table 2). There were significant interactions between depressive disorder and WMH (+) on score changes in the VFT ($P = .024$), sBNT ($P = .045$), TMT-A ($P = .030$), and MMSE ($P = .029$) for the 3-year follow-up period.

Association of the Changes in SGDS Score and WMH Volume With Cognitive Function

Changes in the log WMH volume were related to score changes in the sBNT ($P = .045$), WLMT ($P = .004$), WLRT ($P = .027$), WLRcT ($P = .023$), and TMT-A ($P = .004$), but changes in the SGDS scores were not associated with any neurocognitive tests during the 3-year follow-up period (Table 3). In subjects with depressive disorder at baseline, changes in the SGDS score were not associated with changes

Table 2. Influence of Baseline Depressive Disorder and White Matter Hyperintensities on Changes in the Scores of Neurocognitive Tests During the 3-Year Follow-Up Period

	DEP (+)		WMH (+)		DEP (+) ×WMH (+)	
Neurocognitive Test	*F*	*P* Value[a]	*F*	*P* Value[a]	*F*	*P* Value[a]
Categorical Verbal Fluency Test	11.704	.001	0.084	.773	5.473	.024
15-item Boston Naming Test	3.009	.089	0.245	.623	4.224	.045
Word List Memory Test	5.906	.019	4.502	.039	1.928	.172
Word List Recall Test	3.117	.084	3.181	.081	1.406	.242
Word List Recognition Test	0.004	.951	0.057	.812	0.406	.527
Trail Making Test A	6.015	.018	0.031	.861	4.993	.030
Frontal Assessment Battery	2.651	.110	0.303	.585	2.598	.114
MMSE	6.123	.017	0.043	.836	5.056	.029

[a]Mixed-model ANOVA adjusted for age at baseline, sex, and education.
Abbreviations: DEP (+) = having any major depressive disorder, minor depressive disorder, dysthymic disorder, or subsyndromal depressive disorder; MMSE = Korean version of Mini-Mental State Examination; WMH = white matter hyperintensities; WMH (+) = WMH of grade ≥ 2 on the modified Fazekas scale in deep white matter or subcortical gray matter.

Table 3. Association of the Changes in Short-Form Geriatric Depression Scale (SGDS) Score and Volume of White Matter Hyperintensities With Those in Neurocognitive Test Scores[a] During the 3-Year Follow-Up Period

	All Subjects (n = 54)				Subjects With Depressive Disorder at Baseline (n = 23)				Subjects Without Depressive Disorder at Baseline (n = 31)			
	ΔSGDS		ΔLog V_{WMH}		ΔSGDS		ΔLog V_{WMH}		ΔSGDS		ΔLog V_{WMH}	
Test	β	*P*[a]	β	*P*[a]	β	*P*[a]	β	*P*[a]	β	*P*[a]	β	*P*[a]
ΔVFT	0.082	.560	−0.143	.324	0.088	.682	−0.411	.044	−0.053	.847	0.401	.694
ΔsBNT	0.067	.618	−0.286	.045	0.023	.919	−0.240	.244	0.318	.147	−0.251	.199
ΔWLMT	−0.070	.623	−0.440	.004	0.035	.872	−0.541	.010	−0.197	.463	−0.309	.207
ΔWLRT	−0.131	.366	−0.339	.027	−0.228	.317	−0.437	.040	−0.001	.998	−0.213	.419
ΔWLRcT	−0.048	.740	−0.349	.023	−0.089	.692	−0.443	.036	−0.077	.771	−0.225	.353
ΔTMT-A	−0.073	.607	0.442	.004	−0.198	.298	0.625	.001	−0.513	.080	0.028	.912
ΔFAB	−0.089	.521	−0.155	.281	−0.331	.138	−0.202	.305	−0.030	.914	−0.058	.815
ΔMMSE	−0.070	.641	0.097	.529	−0.124	.585	0.124	.542	−0.048	.862	−0.123	.623

[a]Linear regression model including ΔSGDS, ΔLog V_{WMH}, age, sex, and education as independent variables.
Abbreviations: FAB = Frontal Assessment Battery, MMSE = Korean version of Mini-Mental State Examination, sBNT = 15-item Boston Naming Test, TMT-A = Trail Making Test A, VFT = Categorical Verbal Fluency Test, V_{WMH} = Volume of white matter hyperintensities, WLMT = Word List Memory Test, WLRcT = Word List Recognition Test, WLRT = Word List Recall Test.

in the performances of all neurocognitive tests, whereas changes in the log WMH volume were associated with changes in the performances of the VFT ($P = .044$), WLMT ($P = .010$), WLRT ($P = .040$), WLRcT ($P = .036$), and TMT-A ($P = .001$) for the 3-year follow-up period. In subjects without depression at baseline, changes in the SGDS score and log WMH volume were not associated with changes in the performance of all cognitive tests for the 3 years.

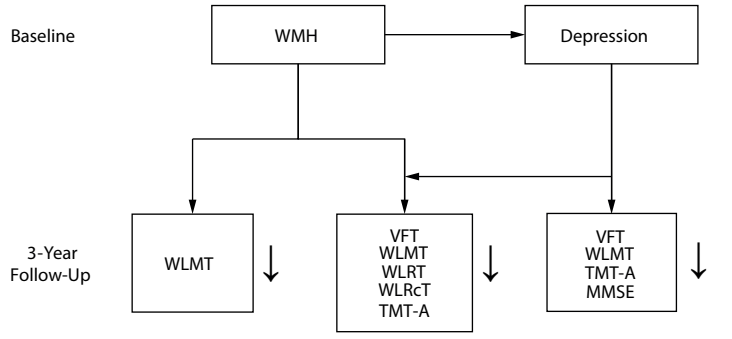
DISCUSSION

Recent systematic reviews demonstrate that moderate cognitive deficits exist in executive function, memory, and attention in patients with depression.[35,36] However, most studies included in the systematic reviews focused only on the effects of depression on cognitive function and did not consider the effects of WMH and interactions between depression and WMH. In many previous studies, WMH was also associated with low performance of diverse cognitive functions, including executive function,[37–39] processing speed,[40–43] memory,[43,44] language,[45] and general cognition.[46,47]

In the current study, baseline depressive disorder was associated with the accelerated cognitive decline over a 3-year follow-up period in various cognitive domains such as verbal fluency, immediate memory, and processing speed while baseline WMH was associated with the accelerated cognitive decline only in immediate memory. Depressive disorder above a definite severity threshold may persistently and broadly influence cognitive function. Many previous studies are in line with our observation. For example, in one study,[35] cognitive dysfunction was present in the remitted unipolar disorder patients, and other studies[48,49] have shown, in particular, that the impairments in executive function, verbal learning, and memory persisted among the remitted patients with depression. In summary, depressive disorder is an independent risk factor for cognitive impairment and decline.

We also found that the presence of depression and WMH interactively influenced the performance of multiple cognitive functions including verbal fluency, naming, and processing speed at the baseline (Table 2 and Figure 1). Interestingly, in subjects with depression at the baseline assessment, decline in multiple cognitive functions during

Figure 2. Link Between Baseline Depressive Disorder, White Matter Hyperintensities, and Changes in the Scores of Neurocognitive Tests Over the 3-Year Follow-Up Period



Abbreviations: MMSE = Korean version of the Mini-Mental State Examination, TMT-A = Trail Making Test A, VFT = Categorical Verbal Fluency Test, WLMT = Word List Memory Test, WLRcT = Word List Recognition Test, WLRT = Word List Recall Test, WMH = white matter hyperintensities.

the 3-year follow-up period was associated with the increase of WMH volume but not with the increase of depressive symptoms. Although in the WMH (–) group the severity of WMH was mild, with grades of less than 2 on the modified Fazekas scale in patients with depression, WMH volume changes were linked with cognitive dysfunction across multiple domains. These findings can be explained in 2 ways. First, WMH may accelerate cognitive decline only when it also induces depression. The depression-executive dysfunction (DED) syndrome was proposed as the clinical expression of frontostriatal dysfunctions that contribute to the development of both depression and executive dysfunction.[50,51] This study further developed the concept of DED syndrome by elucidating the interconnected relationship between depression, WMH, and cognitive dysfunction. Both depression and cognitive function may result from frontostriatal dysfunctions caused by WMH. Second, depression may moderate the impact of WMH on cognitive decline (Figure 2). In the present study, the impacts of WMH volume changes on cognitive decline were not confined to the subjects with vascular depression. The association between WMH volume changes and cognitive decline was also observed in the subjects with nonvascular depression below a definite severity threshold of WMH or with less than 2 on the modified Fazekas scale. This association warrants prospective studies with mediation analyses to further clarify the relationships between depression, WMH, and cognition.

WMH volume changes in patients with depression should be paid careful attention in both clinical and research settings. As depression and WMH are common and coexist frequently in the elderly, the prevention of depression and WMH is one of the best strategies to maintain cognitive function in this population. New strategies that target cognitive symptoms of depression in addition to mood symptoms are needed to improve long-term outcomes of depression.[52] Some propose that treatment of late-life depression may benefit from a cognitive enhancer targeting stimulation of nicotinic acetylcholine receptors, in addition to standard antidepressant medication.[53] Slowing the progression of WMH in the elderly is an important health care issue, and any therapeutic option that may slow the progression of WMH might help to decrease cognitive impairment in the elderly. However, there exists no approved therapy for these brain abnormalities, although a small number of pilot studies show that some blood pressure lowering agents,[54] aspirin,[55] and vitamin B supplementation[56] have delayed the progression of lesions. Large randomized clinical trials dedicated to evaluating the treatments for preventing WMH progression and its clinical correlates are thus urgently needed.

This study has some limitations. First, the follow-up rate in year 3 was low (53.5%), and study participants lost to follow-up were older, less educated, and had higher WMH volume. However, after adjusting for sex, age, and education, there were no differences in the mean scores of neuropsychological tests, SGDS, and WMH volume between those 2 groups. Second, the sample size is relatively small, so it was impossible to observe the longitudinal course of the 4 groups defined by depression and WMH. Third, SSD was included under depressive disorders in this study. There are no settled criteria for SSD, and the criteria for SSD were defined operationally. Further studies are needed to establish the nosology of SSD.

In conclusion, depressive disorder and WMH are interactively associated with the poor performance of multiple cognitive functions. Depressive disorder may moderate future cognitive decline associated with the increase of brain WMH volumes.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: Depression Plays a Moderating Role in the Cognitive Decline Associated With Changes of Brain White Matter Hyperintensities

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List of Supplementary Material for the article

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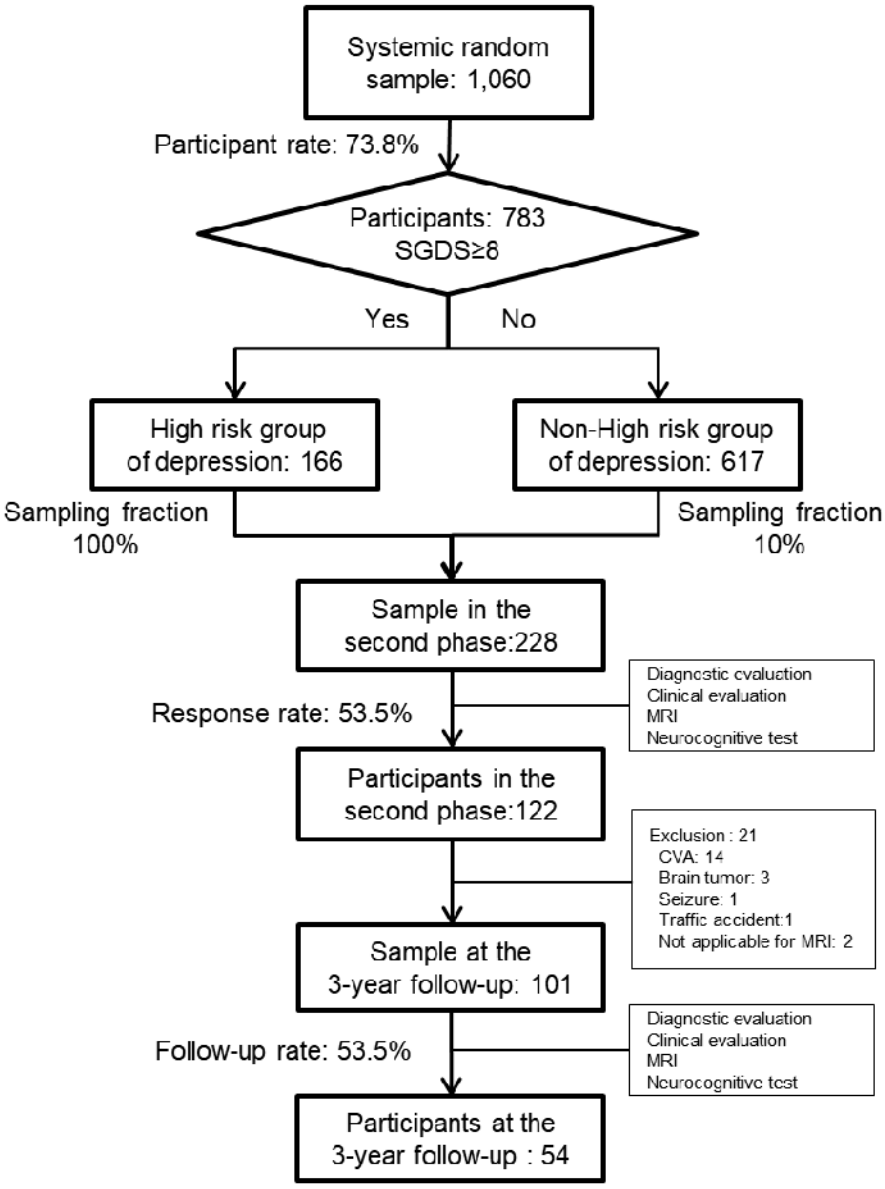
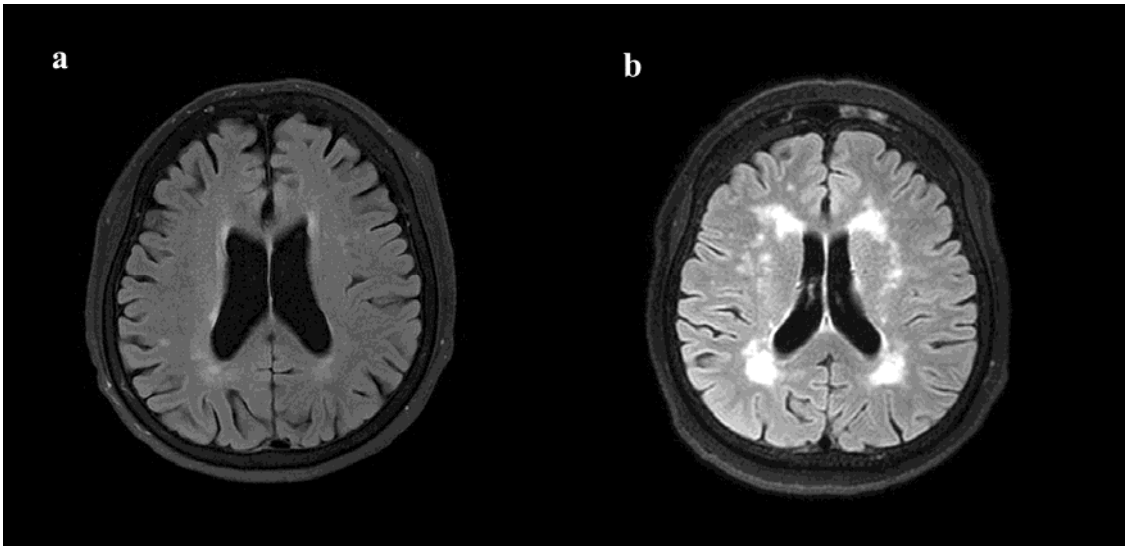
Supplementary eFigure 1. Flowchart of Baseline and 3-Year Follow-up Study



Supplementary eFigure 2. White matter hyperintensities (WMH) on axial images of fluid-attenuated inversion-recovery (FLAIR) MRI



[a]pencil thin lining in periventricular white matter and punctate foci in deep white matter
[b]irregular periventricular WMH extending into deep white matter and beginning confluence of WMH in deep white matter.