

# Neuroanatomic Localization of Magnetic Resonance Imaging Signal Hyperintensities in Geriatric Depression

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**Background and Purpose**—Increased frequency and severity of signal hyperintensities have been regularly reported in elderly depressed patients compared with normal subjects, however, greater neuroanatomic localization of lesions has been limited.

**Methods**—T2-weighted MRI scans in elderly depressed patients (n=35) and normal comparison subjects (n=31) were assessed for signal hyperintensities in lateralized discrete brain regions.

**Results**—Logistic regression revealed that left frontal deep white matter ( $P<.005$ ) and left putaminal ( $P<.04$ ) hyperintensities significantly predicted depressive group assignment.

**Conclusions**—Findings suggest that greater neuroanatomic localization of hyperintensities than heretofore appreciated may relate to late-life depression. (*Stroke*. 1998;29:613-617.)

**Key Words:** depression ■ elderly ■ leukoaraiosis ■ magnetic resonance imaging

Greater severity and/or frequency of subcortical signal hyperintensities on T2-weighted MRI scans have repeatedly been reported in depressed geriatric patients compared with normal elderly control subjects.<sup>1</sup> An increasing number of recent studies implicating these lesions in geriatric depression and some of its clinical features<sup>2-5</sup> support observations that hyperintensities are relevant as a susceptibility factor for and/or correlate of late-life depression.<sup>1,6</sup> In addition to increasing age, presence of cerebrovascular disease risk factors have been most consistently associated with deep white and subcortical gray matter MR signal hyperintensities.<sup>7,8</sup> Furthermore, evidence from imaging/pathological correlation studies in nondepressed subjects indicates that histopathological changes indicative of cerebrovascular disease likely underlie at least the more severe deep white and subcortical gray matter hyperintensities.<sup>9,10</sup> In fact, some investigators consider such lesions “silent cerebral infarcts.”<sup>11</sup> Taken together, these data have contributed to the renaissance<sup>12,13</sup> of an important conceptual entity in geriatric depression that was alluded to 35 years ago<sup>14</sup>: cerebrovascular disease-mediated depression. A critical foundation block supporting this construct are the high rates of depression after stroke, wherein particular relationships with left-sided frontal and basal ganglia infarcts have been demonstrated in many studies.<sup>15</sup> However, in most studies of geriatric depressed patients, ratings of signal hyperintensities have hardly addressed either lesion lateralization or greater anatomic specificity (eg, cortical subdivisions, subcortical gray matter differentiation into thalamus and basal ganglia components), and mixed results with regard to hyperintensity location are common.<sup>1,16</sup> With this in mind, the present study was undertaken with the aim of

examining whether more specific neuroanatomic localization of MR signal hyperintensities in elderly depressed patients suggests particular brain-behavior relationships and supports investigations of poststroke depression that implicate more anterior and left-sided cortical and subcortical abnormalities.

## Subjects and Methods

### Clinical Procedures

Thirty-five elderly depressed patients were consecutively recruited from the Geriatric Psychiatry Service (inpatient, outpatient, and day hospital) at Hillside Hospital, the psychiatric division of Long Island Jewish Medical Center. Thirty-one normal comparison subjects were solicited by means of advertisements in local papers or by word of mouth. All subjects were aged 65 years or older and right-handed, and they were given the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R).<sup>17</sup> Patients met the following inclusion criteria: DSM-III-R<sup>18</sup> major depression (unipolar) and a 21-item Hamilton Depression Rating Scale<sup>19</sup> score of  $\geq 18$ . Exclusion criteria for patients and comparison subjects included presence of a cardiac pacemaker, metallic clips, or other bodily metallic implants or artifacts (because of the MR procedure); acute medical illness or exacerbation of a chronic medical condition; presence of a neurodegenerative disorder, including Alzheimer's disease or a related dementia (subjects did not meet DSM-III-R criteria for dementia); history of transient ischemic attack or stroke; and other past or current DSM-III-R diagnosis (for comparison subjects this included affective disorders). The study was approved by the Long Island Jewish Medical Center Institutional Review Board. After a complete description of the study to the subjects, written informed consent was obtained.

The following clinical and rating scale information was collected for all subjects: history or presence of the cerebrovascular disease risk factors of hypertension, diabetes mellitus, coronary artery disease, and current smoking; scores on the Hamilton Depression Rating Scale<sup>19</sup>

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and the Clinical Global Impression<sup>20</sup> for depression; and age at onset of first depressive episode, defined as admission to a psychiatric hospital or contact with a healthcare professional for evaluation and treatment of sustained depressive symptoms. The above information was obtained by means of direct interview of the patient and significant others as well as from available past medical records.

## MR Procedures

### MRI Acquisition

Subjects were scanned in a 1.0-T whole-body MR system (General Electric) with a dedicated head coil. T2-weighted and intermediate (proton-density) brain images were obtained in the axial plane along the canthomeatal line. The series had a repetition time of 2500 msec and echo delay times of 40 and 80 msec. The sequence provided parallel sections from the base of the skull to the vertex in a 256×256 matrix. Axial images were 5 mm thick, with a 2.5-mm gap between each section. A full coronal series was also obtained but not used for the ratings.

### MR Scan Analysis

Hard copy images were printed for visual quantitative evaluation of signal hyperintensities. MR scans of patients and comparison subjects were combined in a randomized order and independently evaluated under conditions blind to diagnosis by a research psychiatrist (B.S.G.) trained and reliable in hyperintensity recognition and ratings.<sup>5</sup> Hyperintensities were assessed according to the Scheltens rating scale.<sup>21</sup> This semiquantitative scale organizes 7-point, criteria-based ratings of signal hyperintensities that depend on both number and measured size of lesions (0 indicates no abnormalities; 1, <3 mm, n≤5 [where n=number of lesions]; 2, <3 mm, n>6; 3, 4 to 10 mm, n≤5; 4, 4 to 10 mm, n>6; 5, ≥11 mm, n≥1; and 6, confluent lesions). Ratings consider specific neuroanatomic locations/structures in white matter and subcortical gray matter. With use of axial MR images, photographs of brain cuts, and detailed illustrations of approximate slice comparability in neuroanatomy atlases<sup>22,23</sup> to reference and validate brain loci of interest on subject scans, signal hyperintensities were rated on all relevant slices in frontal, parietal, occipital, and temporal deep white matter; and in caudate nucleus, putamen, globus pallidus, thalamus, and internal capsule. All ratings differentiated brain regions into right and left sides. Uncertain or controversial lesion locations on occasional scans were clarified to consensus with another experienced investigator (K.R.R.K.) and/or a neuroradiologist (M.P.). To evaluate interrater reliability for the Scheltens scale, twenty cases (a mixture of depressed patients and comparison subject scans not previously discussed) were randomly selected and independently evaluated by a second rater (K.R.R.K.). As stated in the original description of this instrument, the Scheltens scale is semiquantitative, with a wide range, and as such the  $\kappa$  coefficient for establishing interrater reliability was “judged not to be appropriate” by the authors.<sup>21</sup> Furthermore, because variances in ratings were limited and in many cases were zero, coefficients of agreement often could not be calculated. Therefore, as indicated in Scheltens et al,<sup>21</sup> the analysis of variance for interexaminer reliability study<sup>24</sup> was used. No statistically significant difference between raters on any of the items was observed.

### Statistical Analyses

Demographic and clinical non-MRI variable comparisons were made between depressed patients and control subjects by use of independent univariate *t* tests for continuous variables and  $\chi^2$  tests for analyses of categorical data. Where statistically significant differences existed between groups, such variables were included as covariates in multivariate analyses of covariance (MANCOVA) that examined differences in regional hyperintensity ratings between depressed and control groups. Although the Scheltens 7-point scale is a categorical ordinal scale, it is an anchored scale in which each of the categories actually represents an increase along a continuum of greater severity/frequency of lesions, so that the scale approximates a continuous-interval scale. As such, a parametric MANCOVA was chosen because it inherently protects against type I error when multiple interrelated dependent

variables are compared between groups, and unlike nonparametric tests, it also allows covariance of factors relevant to brain structure that would otherwise confound the interpretation of potential group differences. Logistic regression was then used to develop a model(s) for predicting presence or absence of depression based on hyperintensity ratings in discrete brain loci (right and left deep white matter regions [frontal, parietal, occipital, temporal], and right and left basal ganglia structures [caudate, putamen, globus pallidus, internal capsule] and thalamus). A forward stepwise logistic regression using Wald criteria for inclusion was used to enter hyperintensity variables. Separate logistic regression equations were modeled for all deep white matter ratings (8 variables) and all subcortical (gray matter and internal capsule) ratings (10 variables).

## Results

Clinical and demographic descriptors and comparisons between elderly depressed patients and normal subjects are presented in Table 1. Groups were similar in terms of current age; however there were more females in the depressed group, and a significantly greater proportion of depressed patients than normal comparison subjects had hypertension. Therefore, these variables (gender and hypertension) were included as covariates in MANCOVA in the examination of group differences in regional hyperintensity ratings. Two MANCOVAs were performed that compared depressed patients and control subjects on all lateralized deep white matter structures and on subcortical structures (basal ganglia structures, internal capsule, and thalamus), while covarying for gender and hypertension. MANCOVAs did not reveal significant group differences on hyperintensity ratings, although comparisons between elderly depressed patients and normal control subjects revealed consistently higher raw, unadjusted mean ratings in the depressed group (Table 2). Separate logistic regression analyses for lateralized deep white matter ratings and for lateralized subcortical structure (basal ganglia components, internal capsule, and thalamus) ratings using group classification (depression versus control) as the outcome measure indicated that only left frontal deep white matter (Wald statistic=7.96;  $P<.005$ ; Exp (B)=1.57 [95% confidence intervals, 1.14 to 2.10]) and left putamen (Wald statistic=4.65;  $P<.04$ ; Exp (B)=1.54 [95% confidence intervals, 1.03 to 2.20]) hyperintensities significantly predicted depression. The model wherein left frontal deep white matter hyperintensities were found to be a significant predictor of depression group assignment had a sensitivity of 59% and specificity of 84%. The model identifying left putaminal hyperintensities as a significant predictor of depression had a sensitivity of 62% and specificity of 58%.

## Discussion

To our knowledge, this is the first demonstration in a controlled study that a more anatomically precise localization of deep white matter hyperintensities (left frontal lobe location) is associated with major depression in the elderly. Among the many investigations addressing signal hyperintensities in geriatric depression,<sup>1</sup> two studies are especially relevant. A pilot study of 12 older depressives and 12 healthy control subjects examined deep white matter hyperintensities in *nonlateralized* frontal, parietal, occipital, and temporal regions, and with use of a 3-point rating system (punctate, multipunctate, and diffuse), did not demonstrate differences between groups.<sup>25</sup> A more recent investigation with a larger sample size rated lesions

**TABLE 1. Clinical and Demographic Characteristics of Depressed Patients and Normal Comparison Subjects**

Characteristic	Depressed Patients, n=35		Normal Comparison Subjects, n=31		P*
	Mean	SD	Mean	SD	
Age, y	74.7	6.4	72.9	4.7	.19
Age at onset of illness, y	56.5	17.1	...	...	...
Hamilton Depression Rating Scale score	27.0	5.7	3.0	2.3	<.0001
Clinical Global Impression for Depression score	4.7	0.7	1.1	0.3	<.0001
	Percent Distribution				
	n	%	n	%	P†
Sex distribution					
Male	9	26	18	58	<.01
Female	26	74	13	42	
Cerebrovascular risk factors					
Hypertension	22	63	6	19	<.001
Coronary artery disease	11	31	7	23	0.60
Diabetes mellitus	2	6	2	6	1.00
Current smoker	0	0	0	0	1.00

\*By *t* test.†By  $\chi^2$  test.

as present or absent in the left and right frontal, parietal, occipital, and temporal regions; no significant group differences were reported.<sup>4</sup> However, the present investigation used a more complex and explicit rating schema that meticulously considers both number and size of lesions in each subregion.

In this investigation, left putamen hyperintensities also predicted depression group assignment. We are not aware of other studies of elderly depressives that have rated hyperintensities in lateralized or nonlateralized basal ganglia subcomponents and thalamus. However, the left putamen finding is consistent with another controlled study that reported a relationship between the presence of hyperintensities in the left total basal ganglia and late-life depression.<sup>4</sup> Histopathologic correlates of hyperintensities in elderly depressives have not been investigated. However, in older patients, larger hyperintensities in central gray matter have been demonstrated in MR/pathological correlation studies to represent lacunar infarctions, which classically refer to occlusion of penetrating vessels secondary to atheromata, lipohyalinosis, fibrinoid necrosis, and embolization.<sup>9</sup> The putamina are the most common sites for lacunar infarctions,<sup>26</sup> possibly because they are situated at relatively greater distance from the origins of the penetrating arteries responsible for their blood supply.<sup>27</sup> Among subcortical gray matter structures examined in this study, hyperintensity ratings were greatest in the putamen in both depressed patients and control subjects.

The present results in geriatric depressives without transient ischemic attacks or stroke implicate possible “silent stroke” lesions<sup>11,28</sup> (ie, hyperintensities) occurring in brain regions (left frontal lobe, left putamen) that are remarkably similar to infarct locations reported in stroke patients with poststroke depression.<sup>15</sup> As such, hypotheses that invoke a cerebrovascular etiology or contribution in some late-life depressives<sup>29,30</sup> are

buttressed. This suggests that health strategies aimed at preventing cerebrovascular disease (eg, diet, physical activity/exercise, smoking cessation, and cardiovascular medication compliance)<sup>31</sup> may also lessen eventual depressive vulnerability in the elderly. Current findings additionally provide support for the strategic importance of left frontal lobe and basal ganglia abnormalities in depression and for previously described pathophysiological models of depression based on frontal-striatal circuit abnormalities.<sup>15,32–36</sup>

Because hypertension was overrepresented in the depressed patients compared with the normal subjects of this study and since hypertension is a risk factor for hyperintensities,<sup>8</sup> current findings allow speculation about a possible relation between hypertension and depression in the elderly that is potentially mediated through hypertension-related cerebrovascular changes in brain regions associated with mood regulation. However, other hypertension factors could also relate to depression; hence, a methodological limitation of this study is that patients and normal comparison subjects were not matched for the presence or absence of hypertension, although hypertension was statistically controlled for in the multivariate analyses. Planned extension of MR hyperintensity investigation in depressed versus nondepressed elderly hypertensives should further elucidate relationships among hypertension, depression, and hyperintensities and their distribution in the brain.

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**TABLE 2. MR Hyperintensity Ratings\* of Elderly Depressed Patients and Normal Comparison Subjects**

Variable	Depressed Patients, n=35		Normal Comparison Subjects n=31	
	Mean	SD	Mean	SD
Deep white matter hyperintensities				
Frontal region				
Right	2.47	2.21	1.42	2.01
Left	2.29	2.10	0.84	1.53
Parietal region				
Right	1.56	2.06	0.71	1.27
Left	1.65	2.14	0.52	1.03
Occipital region				
Right	1.73	2.11	0.97	1.60
Left	1.94	2.19	1.13	1.73
Temporal region				
Right	0.42	0.98	0.03	0.18
Left	0.21	0.73	0.13	0.56
Subcortical gray matter hyperintensities				
Caudate				
Right	0.71	1.06	0.42	0.67
Left	0.56	1.11	0.26	0.44
Putamen				
Right	1.21	1.59	0.81	1.11
Left	1.56	1.67	0.75	1.09
Globus pallidus				
Right	0.88	1.18	0.52	0.96
Left	0.62	0.98	0.52	1.03
Thalamus				
Right	0.56	0.99	0.26	0.63
Left	0.74	1.14	0.48	1.03
Internal capsule				
Right	0.09	0.29	0.22	0.76
Left	0.18	0.72	0.16	0.58

\*Based on the Scheltens 7-point scale (see text).

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