Gray Matter Atrophy in Patients With Ischemic Stroke With Cognitive Impairment

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Background and Purpose—Patients with ischemic stroke are at risk for developing vascular cognitive impairment ranging from mild impairments to dementia. MRI findings of infarction, white matter hyperintensities, and global cerebral atrophy have been implicated in the development of vascular cognitive impairment. The present study investigated regional gray matter volume differences between patients with ischemic stroke with no cognitive impairment and those with impairment in at least one domain of cognitive function.

Methods—Ninety-one patients with ischemic stroke participated. Detailed neuropsychological testing was used to characterize cognitive functioning in 7 domains: orientation, attention, working memory, language, visuospatial ability, psychomotor speed, and memory. High-resolution T1-weighted 3-dimensional fast-spoiled gradient recalled structural MRIs were processed using optimized voxel-based morphomery techniques while controlling for lesions. Whole brain voxelwise regional differences in gray matter volume were assessed between patients with stroke with no impaired cognitive domains and patients with stroke with at least one impaired cognitive domain. Logistic regression models were used to assess the contribution of demographic variables, stroke-related variables, and voxel-based morphometry results to classification of cognitive impairment group membership.

Results—Fifty-one patients had no impairments in any cognitive domain and 40 patients were impaired in at least one cognitive domain. Logistic regression identified significant contributions to cognitive impairment groups for demographic variables, stroke-related variables, and cognitive domain performance. Voxel-based morphology results demonstrated significant gray matter volume reductions in patients with stroke with one or more cognitive domain impairment compared with patients with stroke without cognitive impairment that was seen mostly in the thalamus with smaller reductions found in the cingulate gyrus and frontal, temporal, parietal, and occipital lobes. These reductions were present after controlling for group differences in age, education, stroke volume, and laterality of stroke. The addition of voxel-based morphometry-derived thalamic volume significantly improved a logistic regression model predicting cognitive impairment group membership when added to demographic variables, stroke-related variables, and cognitive domain performance.

Conclusions—These results suggest a central role for the thalamus and lesser roles for other cortical regions in the development of cognitive impairment after ischemic stroke. Indeed, consideration of thalamic volumes adds significant information to the classification of cognitive impaired versus nonimpaired groups beyond information provided by demographic, stroke-related, and cognitive performance measures. (Stroke. 2008;39:785-793.)

Key Words: cognition disorders ■ MRI ■ vascular cognitive impairment

Patients with ischemic stroke are at increased risk of developing vascular cognitive impairment, which ranges in severity from mild and/or isolated cognitive impairment to vascular dementia.1 Vascular cognitive impairment may affect half of all stroke survivors.2 The prevalence of vascular cognitive impairment has been estimated to be 50 per 1000 population with a higher prevalence of mild or isolated impairment (26 per 1000) compared with vascular dementia (15 per 1000).3 Studies demonstrate similar rates of institutionalization, mortality, and other adverse outcomes among patients with stroke with cognitive impairment but no dementia and patients with stroke with dementia.3 In addition,
patients with stroke with cognitive impairment but no dementia have an increased 5-year risk of developing vascular dementia or other dementias. If patients with stroke with cognitive impairment but no dementia are at increased risk of dementia, identification of markers for developing cognitive impairment might prove useful for interventions designed to prevent the progression to vascular dementia.

Involvement of the thalamus in cognitive disturbances is well established. Impairments in sensory function, motor abilities, language, executive function, and long-term memory are associated with vascular syndromes in the thalamus. In a study of 10 patients with isolated thalamic lesions, impairments in long-term memory were associated with lesions of the mammillothalamic tract and impairments in working memory were associated with lesions of the medial dorsal, midline, and intralaminar nuclei. Strategic lesions of the thalamus were found to be related to the development of vascular dementia in 8 patients after infarction of the paramedian nucleus and the anterior nucleus. These findings suggest that the precise location of thalamic lesions influences the type of cognitive deficit observed.

General cerebral atrophy has also been associated with the development of cognitive impairment after stroke. Cortical gray matter atrophy correlated with dementia severity in a sample of patients with subcortical ischemic vascular disease and was an independent predictor of cognitive decline in a sample of patients with subcortical cerebrovascular brain injury. The exact mechanism of this atrophy is not known but may reflect secondary degeneration after ischemic events. Voxel-based morphometry (VBM) provides an automated, voxelwise comparison of gray matter volume between groups. The procedure involves the normalization of individual subjects’ MRI to a common template so that group comparisons can be conducted. Because the individual MRIs are registered into the same space, they can be combined into relevant groups and compared. Since no a priori regions of interest are defined, VBM provides an unbiased whole brain comparison between groups, making it an ideal method for exploratory cross-sectional studies. As VBM techniques require the warping of individual brains to a common template, the presence of lesions may result in incorrect tissue type classifications at the site of the lesion during this normalization process. One method of adjusting for the presence of lesions during normalization is to mask out the lesions from consideration during the warping process so as to remove the influence of the lesions in the calculations of the required image warping. This process allows for the calculation of parameters required to accurately normalize individual lesioned brains to a template without the potentially confounding influence of the infarcted tissue. The normalizing parameters developed from the lesion-masked scans can then be applied to the scans with the lesions unmasked. In the present study, we used whole brain, voxel-based analyses to investigate regional differences in gray matter volume in a sample of patients with ischemic stroke without cognitive impairment compared with those with impairment in one or more cognitive domains. We used a cost–function technique to adjust the warping of individual brains to a common template. We sought to determine the usefulness of this approach to classifying gray matter changes after ischemic stroke and to better understand the relationship between gray matter changes and cognitive function.

Materials and Methods

Participants
Participants were patients with ischemic stroke who presented to the Stroke and Neurologic Critical Care Service at Rush University Medical Center. The study was explained to all potential participants and their families while they were inpatients at the time of stroke. Those who met study criteria and who agreed to be contacted at a later date were asked to participate once they entered the 3- to 6-month poststroke time window. A priori inclusion criteria were age 50 or older (including persons closer to age 50 than 49); ischemic stroke defined by the National Institute of Neurological and Communicative Disorders and Stroke Data Bank criteria 3 to 6 months before study entry; sufficient English language skills for psychological testing; and availability of a proxy or relative knowledgeable about the participant. Standard clinical CT or MRI scans during hospitalization were available and used in stroke subtyping and in ruling out cerebral hemorrhage. Approximately one third of potential subjects approached agreed to participate; exact numbers of nonparticipants and a comparison of persons who did and did not participate was not possible, because Institutional Review Board regulations prevented the gathering of nonparticipant data.

Exclusion criteria included patients with aphasia who scored less than 50% correct on the Boston Diagnostic Aphasia Examination Commands Subtest or who otherwise could not complete psychological testing because of a language disorder; diagnosed chronic or degenerative disease or condition before stroke affecting the central nervous system (eg, Alzheimer disease); active substance abuse disorders as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; intracranial hemorrhage; difficult to control epilepsy that could present with cognitive impairment; or temporal lobe epilepsy. In addition, patients with temporal lobe stroke were excluded because the study original hypotheses sought to compare Alzheimer disease markers (eg, medial temporal lobe atrophy) to markers of cerebral vascular disease. Three patients, who otherwise met study participation requirements, were excluded due to the presence of temporal lobe infarcts. Prior stroke was not exclusionary. Although patients with preexisting Alzheimer disease or other diagnosed neurodegenerative conditions were excluded, exclusion criteria did not include the presence of undiagnosed prestroke cognitive impairment. The study was completed under the guidance and approval of the Institutional Review Board at Rush University Medical Center and the University of Illinois at Chicago.

Study Instruments and Examination Procedures
All study participants completed formal neuropsychological assessment administered by a trained neuropsychological technician under the supervision of the study neuropsychologist. The examination took approximately 90 to 120 minutes to administer and included the following tests: Boston Diagnostic Aphasia Examination, Com- mands subtest; Controlled Learning and Enhanced Recall, Immediate and Delayed; Self-Ordered Pointing Task; Wechsler Memory Scale, Third Edition: Paragraph I and Digit Span subtests; Wechsler Memory Scale, Form I Mental Control; Symbol Digit (Oral Version); portions of the Behavioral Dyscontrol Scale; Mini-Mental State Examination; Figural Recognition Test; CERAD Boston Naming Test and Verbal Fluency; Brief version of the Ravens Progressive Matrices; Grooved Pegboard Test; the Chicago Multiscale Depression Inventory; and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as an estimate of change in cognitive function from premorbid levels.

The subjects also completed an unstructured neurologic interview to determine history of, number of, timing, symptoms, and recovery from stroke; a history of memory loss and other symptoms of dementia; and a structured neurologic interview to determine the history of dementia onset and symptoms of cognitive dysfunction.
Table 1. Neuropsychological Test Scores (means [SDs]), Listed by Domain, and Compared Across Patients With and Without Cognitive Impairment

<table>
<thead>
<tr>
<th>Tests Listed by Domain</th>
<th>Patients Without Cognitive Impairment</th>
<th>Patients With Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation MMSE Orientation Items</td>
<td>9.66 (0.55)†</td>
<td>9.03 (1.28)</td>
</tr>
<tr>
<td>Attention Digits Forward</td>
<td>6.26 (1.08)*</td>
<td>5.58 (1.44)</td>
</tr>
<tr>
<td>Working Memory CLTR Total Immediate Recall</td>
<td>30.96 (6.03)‡</td>
<td>23.32 (6.64)</td>
</tr>
<tr>
<td>Language Boston Naming Test</td>
<td>14.43 (0.97)‡</td>
<td>12.82 (2.46)</td>
</tr>
<tr>
<td>Vissuospatial Animal Naming</td>
<td>17.7 (4.82)‡</td>
<td>12.89 (5.99)</td>
</tr>
<tr>
<td>Visuospatial Figural Recognition Test</td>
<td>8.00 (0.00)*</td>
<td>7.68 (0.90)</td>
</tr>
<tr>
<td>Psychomotor Raven’s Matrices</td>
<td>11.94 (1.34)‡</td>
<td>10.08 (2.37)</td>
</tr>
<tr>
<td>Memory Grooved Pecs Domain (pegs/sec)</td>
<td>0.25 (0.07)‡</td>
<td>0.17 (0.09)</td>
</tr>
<tr>
<td>Memory Symbol Digit Oral Score</td>
<td>42.46 (11.03)‡</td>
<td>28.03 (11.46)</td>
</tr>
<tr>
<td>Memory CLTR Total Immediate Recall</td>
<td>30.96 (6.03)‡</td>
<td>23.32 (6.64)</td>
</tr>
<tr>
<td>Memory CLTR Delayed Recall</td>
<td>12.38 (2.32)‡</td>
<td>8.95 (3.16)</td>
</tr>
<tr>
<td>Memory WMS Paragraph Immediate Recall</td>
<td>13.08 (3.56)‡</td>
<td>9.08 (4.05)</td>
</tr>
<tr>
<td>Memory WMS Paragraph Delayed Recall</td>
<td>11.74 (3.28)‡</td>
<td>6.97 (3.99)</td>
</tr>
</tbody>
</table>

*P<0.05.
†P<0.01.
‡P<0.001.

MRI Image Acquisition

All MRIs were acquired using a 1.5-Tesla General Electric Signa scanner (General Electric Medical Systems, Milwaukee, Wis) at Rush University Medical Center. A high-resolution 3-dimensional spoiled gradient recalled T1-weighted MRI scan was acquired for each subject. One hundred twenty-four gapless coronal slices with a thickness of 1.6 mm were obtained with the following parameters: repetition time 34 ms, minimum echo time 7 ms, one acquisition, flip angle 35, matrix size 256×192, field of view 22 cm, and inplane resolution 0.8594 mm. Additionally, a coronal 3-dimensional fast spin echo T2-weighted MRI scan was acquired with the following parameters: repetition time 2900 ms, echo time 102 ms, 2 acquisitions, matrix size 256×192, field of view 22 cm, slice thickness 3.0 mm with no gap, 48 slices, and inplane resolution 0.8594 mm.

Lesion Identification

The study neurologist (P.B.G.) classified the etiologies of the presenting strokes at the time of study entry using Stroke Data Bank Criteria and the total number of visible lesions, including both the lesion from the presenting stroke and those from previous stroke events, were counted using Cardiovascular Health Study criteria. The lesion volumes were traced on the axial, coronal, and sagittal orientations of 3-dimensional T1 spoiled gradient recalled scans using the Analyze Software package (Analyze, Mayo Clinic Foundation, Rochester, Minn). The 3-dimensional T2 fast spin echo scans were used to assist in identifying the lesions and tracing the lesion volume. The lesion maps were saved in a format acceptable for VBM processing.

Voxel-Based Morphometry Image Preprocessing

Images were analyzed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6.5 (Mathworks, Natick, Mass). A modified optimized VBM technique was used following the method of Good and colleagues. We used a cost–function modification of the optimized VBM technique to adjust for the presence of infarcted tissue during VBM processing. Because infarcted tissue leads to tissue misclassification, the presence of lesions can affect calculation of segmentation and normalization parameters required in VBM. The cost–function modification removes infarcted tissue from the calculation of these parameters, thus removing the potential for tissue misclassification during segmentation and normalization.

The first step in VBM processing involved the construction of a customized sample-specific brain template. This template was developed by using the lesion maps identifying the volume and locations of infarcts to mask out these regions on the individual 3-dimensional T1 spoiled gradient recalled volumes and normalizing the lesion-masked volumes of all participants to the standard brain template of the Montreal Neurological Institute using a 12-parameter affine transformation with nonlinear adjustments with 7×7×7 basis functions. Masking the lesions from the individual volumes removed the potential misclassification of tissue type during the affine transformation and nonlinear adjustments. The spatial transformation parameters for this normalization were then applied to the individual nonmasked volumes and the resultant normalized images were resampled to a 1×1×1-mm voxel size smoothed with a 8-mm full width half maximum Gaussian kernel and then averaged to produce the sample-specific whole brain template. Templates for gray matter, white matter, and cerebrospinal fluid were computed by segmenting the sample-specific whole brain template into the 3 components based on image intensity classification and probability of tissue class membership.
The second step in VBM processing involved the normalization of individual scans to the sample-specific template. The individual 3-dimensional T1 spoiled gradient recalled scans were masked for lesions and segmented into gray matter, white matter, and cerebrospinal fluid components using information from the sample-specific tissue classification templates. The individual gray matter segments were spatially normalized to the sample-specific gray matter template created during the sample-specific template creation using a 12-parameter affine transformation and nonlinear adjustments with 7×8×7 basis functions. Masking out the location of infaracts allowed for the calculation of tissue segmentation and normalization parameters absent the potential for tissue misclassification and normalization distortion induced by the presence of the lesions. The spatial transformation parameters obtained from the lesion-masked gray matter normalization were applied to the nonmasked 3-dimensional T1 spoiled gradient recalled volumes and resampled to a 1×1×1-mm voxel size to produce lesion-adjusted normalized volumes. Individual lesion-adjusted normalized whole brain volumes were then segmented again into gray matter, white matter, and cerebrospinal fluid partitions using a Markov random field model to improve tissue type classification. As a consequence of spatial normalization, the volumes of some regions may increase or decrease in size. To correct for these volume changes, the normalized gray and white matter segments were modulated to preserve the amount of tissue from the nonnormalized gray and white matter segments. In the modulation step, voxel values are multiplied by the Jacobian determinants derived from the normalization process. The segmented, normalized, and modulated individual lesion-adjusted brain segments were smoothed with an 8-mm full width half maximum Gaussian kernel. Application of the smoothing kernel compensates for interindividual variability and conforms the data more closely to Gaussian random field theory, which provides for corrected statistical inference.

**Statistical Analyses**

Group differences in demographic and stroke-related variables and cognitive performance domain scores were assessed using a 2-sample *t* test or χ² test where appropriate. The segmented, normalized, modulated, smoothed lesion-adjusted MRI images were analyzed in SPM2 to evaluate gray matter differences between the patients with no cognitive impairment and patients with impairment in one or more cognitive domains. A binary logistic regression was used to assess the relative contributions of each cognitive domain to the classification of no cognitive impairment/at least one impaired cognitive domain after controlling for group differences in demographic and stroke-related variables. To assess regional differences in gray matter volume between the 2 groups, voxel-by-voxel contrasts were performed using the general linear model controlling for total brain volume and selected stroke-related, cognitive, and demographic variables. Significant differences in gray matter tissue volume between the groups were detected at a statistical threshold of *P* < 0.005. Additionally, clusters of significant differences were required to have an extent of at least 50 voxels. To assess if gray matter volume differences significantly increased the accuracy of classification of participants to cognitive impairment groups above that obtained with cognitive performance measures alone, the binary logistic regression was repeated with gray matter volume values added to the list of independent variables.

**Results**

One hundred four participants were enrolled. MRI scans were available on 91 of the subjects (3 scans missing due to subject refusal, 4 due to severe movement artifact, and 6 due to technical failure). Results for these 91 examinations are presented.

Etiologies of the presenting strokes at the time of study entry were determined using Stroke Data Bank Criteria. Infarctions due to atherosclerosis or tandem arterial pathology accounted for 26.6% of the strokes, 23% were classified as lacunar infarctions, 4.3% as cardiac emboli, 4.3% as infarctions of unknown cause, and 41.5% as unknown. Lesion locations were 28.7% in the left hemisphere, 36.2% in the right hemisphere, 9.6% in the brain stem, 10.6% in the pons, and 14.9% of the locations were unknown. Cardiovascular Health Study criteria were used to count the total number of visible lesions. The number of lesions ranged from 0 to 8 with an average of 1.63 (SD, 1.78) per subject. Cortical lesions were present in 26.9% of the participants and 44.1% had at least one subcortical lesion.

Fifty-one of the 91 subjects were unimpaired in any cognitive domain with the remaining 40 impaired in one or more cognitive domains. The cognitively impaired group had the following distribution of involved domains: 4.3% impaired orientation, 6.4% impaired attention, 9.6% impaired working memory, 8.5% impaired language, 3.2% impaired visuospatial abilities, 25.5% impaired psychomotor speed, and 13.9% impaired declarative memory. The nonimpaired and impaired groups did not differ in gender distribution, handedness, total number of strokes, number of cortical strokes, number of subcortical strokes, or estimated change from premorbid function. The cognitively impaired group was significantly older, had fewer years of formal education, more left-sided strokes, lower mental status scores, and increased stroke volume compared with the noncognitive-impaired group. Gray matter, white matter, and cerebrospinal fluid volumes, derived from the VBM processing, were not significantly different between the groups (Table 2). Contribution of cognitive domain performance to group classification was examined using a binary logistic regression. In this model, demographic and stroke-related variables demonstrating significant group differences were entered as a first block of variables (age, years of education, presence of left-sided stroke, and total lesion volume) with cognitive domain performance entered as a second block of variables. The overall model was significant (χ² = 52.42, *P* = 0.0005) with only psychomotor processing speed cognitive domain performance significantly determining the model (Wald = 6.59, *P* = 0.01).

Examination of VBM-derived gray matter volume differences was conducted using the analysis of covariance model in SPM2. Age, years of education, presence of left-sided strokes, total brain volume, and total lesion volume were entered as covariates of no interest. Decreased gray matter volume was detected in the cognitively impaired group compared with the unimpaired group in multiple regions, but mostly in the bilateral thalamus. Additional regions of decreased gray matter volume in the cognitive impairment group were found in the bilateral superior, middle and medial frontal lobes, the right superior temporal lobe, the bilateral middle temporal lobes, the right central gyrus, the right anterior cingulate gyrus, the left posterior cingulate gyrus, bilateral inferior parietal lobe, the left cuneus, the bilateral precuneus, the left superior occipital lobe, and the right lingual gyrus. No regions of decreased gray matter volume were detected in the noncognitive-impaired group compared with the cognitive impairment group (Table 3; Figure). Although many regions were identified as having decreased gray matter volume in the cognitive impairment group, the
majority of differences were in the bilateral thalamus. Indeed, there were over 5100 voxels in the thalamus demonstrating a significant loss of volume compared with the right post central gyrus, which had less than 2000 such voxels. Six subjects had radiologically confirmed thalamic lesions (3 no cognitive impairment, 3 cognitive impairment). These patients were excluded and the VBM analyses were recomputed without significantly altering the results (Table 3; Figure).

The distribution of thalamic sub nuclei involvement was examined by using the Talairach Daemon (http://ric.uthscsa.edu/projects/talairachdaemon), which provides structural locations based on Talairach coordinates. Significantly decreased gray matter volumes in thalamic subnuclei in the cognitive impairment group compared with the noncognitive-impaired group were found in the left medial dorsal nucleus, ventral lateral nucleus, ventral anterior nucleus, and pulvinar.

Individual participants’ normalized gray matter volume values were extracted from the thalamic regions demonstrating significant group differences on SPM analyses. As expected, these values were significantly lower in patients with cognitive impairment compared with patients without cognitive impairment (no cognitive impairment mean = 0.264 [0.044]; cognitive impairment mean [SD] = 0.210 [0.054]; F[21, 89] = 27.32, P < 0.0005).

To assess if thalamic volume provided additional information for cognitive group classification, beyond that found for demographic, stroke-related, and cognitive domain performance, the binary logistic model analyzing the contribution of these variables was repeated with thalamic volume included in the analysis. For this binary logistic regression, demographic and stroke-related variables were entered first in the model, cognitive domain performance scores were entered second in the model, and normalized thalamic gray matter volume was entered last in the model. As previously found, demographic and stroke-related variables significantly contributed to the model (model $\chi^2_{214} = 12.65, P = 0.013$) with a significant increase in the model accuracy with the addition of the cognitive domain performance measures (model $\chi^2_{52.41} = 5.41, P < 0.0005$). Importantly, the addition of thalamic gray matter volume significantly improved the model using only demographic, stroke-related, and cognitive domain performance (model $\chi^2_{214} = 63.95, P < 0.0005$). Of all the variables entered in the final model, normalized thalamic volume provided the greatest separation between patients with any cognitive impairment and patients with no cognitive impairment (Wald$^2 = 6.50, P = 0.01$). The next most discriminating variable was psychomotor speed cognitive domain performance (Wald$^2 = 5.44, P = 0.02$) followed by patient age (Wald$^2 = 5.14, P = 0.02$) and spatial cognitive domain performance (Wald$^2 = 4.06, P = 0.04$).

**Discussion**

In the present study, gray matter volume was compared between patients with ischemic stroke with no cognitive impairment and patients with impairment in one or more cognitive domains. The cognitively impaired group was older, had fewer years of education, more left-sided strokes, greater lesion volumes, and deficits in multiple cognitive domains, including orientation, attention, working memory, language, visuospatial skills, psychomotor speed, and memory. Given these variables, patient psychomotor processing speed cognitive domain demonstrated the strongest relationship to the cognitive impairment classification.

In addition, we found significant decreases in gray matter volume in patients with ischemic stroke with cognitive impairment compared with those without impaired cognitive functioning in the thalamus, frontal, temporal, parietal, and occipital lobes. The major region of decreased gray matter volume was in the thalamus. These differences were not due to effects of age, educational levels, presence of left-sided lesions, total lesion volume, total brain volume, nor differences in change from premorbid function. Instead, the decreased gray matter volume appears to relate to differences in cognitive status as reflected by performance on neuropsychological tests.

The vast majority of gray matter reduction in the cognitive impairment group was in the thalamus. This reduction in gray matter volume reflected group differences in multiple cognitive domains, including orientation, attention, working memory, visuospatial abilities, language, and declarative memory.
The nature of these relationships suggests that as thalamic integrity is affected, cognitive performance suffers. The wide spectrum of affected cognitive domains reflects the multimodal nature of thalamic relays throughout the brain. Rather than finding isolated thalamic volume–cognitive relationships, relationships to multiple cognitive behaviors with frontal lobe function and temporal lobe function were noted. This suggests that thalamic damage after ischemic stroke may lead to deficits in multiple cognitive domains, which might ultimately manifest in a diagnosis of dementia.

The specific relationship between VBM-derived thalamic gray matter volume and cognitive impairment in ischemic stroke has not been previously reported to our knowledge. Prior studies have investigated cortical gray matter volume and have found it to be predictive of the presence of cognitive impairment as well as the rate of cognitive decline. These studies, however, did not investigate subcortical gray matter volumes.

One previous study investigated whole brain gray matter volume in patients with ischemic stroke in the acute and chronic phases of stroke. Although cognitive function was not assessed, this study did note a shrinkage in brain tissue from acute to chronic phases. This shrinkage was present in the area of radiologically identified lesions, contralateral homologous regions, and in the striatum and thalamus. The shrinkage in the striatum and thalamus was not related to lesion size and was suggested to be independent of the ischemic event.

Additional evidence of thalamic involvement in cognitive impairment after stroke is found in studies of patients with concomitant Alzheimer disease. Patients with neuropathologically confirmed Alzheimer disease were likely to have...
greater cognitive impairment in the presence of infarcts in the thalamus, basal ganglia, and deep white matter. Even in patients without significant neuropathological evidence of Alzheimer disease, the presence of thalamic lacunes was associated with lower cognitive function during life. Thalamic involvement in cognitive function is also found in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Diffusion tensor imaging studies have found evidence of decreased white and gray matter integrity in the thalamus in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy with and without dementia. In these studies, measures of thalamic integrity correlated with cognitive performance measures of general mental status, general IQ, and executive function. The abnormalities in gray and white matter integrity appeared to be unrelated to frank infarctions, but rather, reflected secondary degeneration due to disruption of distant tissue.

Our finding of decreased thalamic gray matter volume in the patients with stroke with impaired cognitive function compared with patients with stroke without cognitive impairment after controlling for differences in age, educational level, presence of left-sided strokes, total brain volume, or the volume of ischemic lesions suggests that the damage to thalamic tissue was not due to primary stroke effects, but rather may be secondary to degenerative processes. Given the

**Figure.** Regions of significant decreased gray matter volume in patients with ischemic stroke with impaired performance in one or more cognitive domains compared with patients with ischemic stroke with no cognitive impairment. Differences in volume values were corrected for group differences in age, educational level, presence of left-sided strokes, total brain volume, and total stroke lesion volumes in an analysis of covariance model. Voxels evidencing significant decrease in the cognitive impairment group are displayed on representative coronal sections (number represents the y plane of Talairach coordinates) of an average T1-weighted brain image created from the sample scans. The color scale indicates the magnitude of T values with lowest appearing in dark red and the highest in bright yellow/white. The left side of the images represents the left side of the brain.
central role of the thalamus as a gateway to the cerebral hemispheres, damage to widely dispersed cortical regions might well result in secondary atrophy to this structure. Regardless of the cause, decreased thalamic gray matter volume was related to cognitive status as measures by a wide spectrum of cognitive function measures and provided information that significantly improved a classification model of cognitive impairment based on demographic variables, stroke-related data, and cognitive domain performance alone.

The application of VBM methodologies to ischemic stroke cases could be problematic. Infarcted tissue misclassification during the segmentation process could falsely contribute to gray matter, white matter, or cerebrospinal fluid compartments. In the present study, however, we used a cost–function technique that removes the infarcted tissue from the classification of tissue type and determination of normalization parameters. By removing these lesions from the VBM determination of segmentation and normalization parameters, the tissue classification and image warping are unaffected. An additional concern with any VBM study is the accuracy of the tissue classification and determination of normalization. In the present study, however, we used a cost–function that significantly improved a classification model of cognitive impairment based on demographic variables, stroke-related data, and cognitive domain performance alone.

The application of VBM methodologies to ischemic stroke cases could be problematic. Although such an effect may be present in our study, we used a cost–function technique that removes the infarcted tissue from the classification of tissue type and determination of normalization parameters. By removing these lesions from the VBM determination of segmentation and normalization parameters, the tissue classification and image warping are unaffected. An additional concern with any VBM study is the accuracy of the normalization process. Voxel-based morphometry methodologies depend on warping native images into a common space. Such warping techniques may be associated with decreasing accuracy as the algorithm proceeds from central to peripheral structures. Although such an effect may be present in our results, we do identify many structural differences in the periphery between patients with stroke with and without cognitive impairment, suggesting a minimal effect. Additionally, our findings of significant gray matter volume differences in patients with stroke with at least one impaired cognitive domain do not necessarily demonstrate a casual relationship between loss of thalamic volume and development of cognitive impairment. A longitudinal design would be more adept at demonstrating such a casual relationship.

These results are based on a single sample of patients with ischemic stroke with and without cognitive impairment. The sample is drawn from a large tertiary university hospital, not all persons who were approached participated, and although persons diagnosed with Alzheimer disease before their stroke were excluded from participation, we cannot rule out the presence of Alzheimer disease pathology or other sources of prestroke cognitive decline in our sample. In addition, we excluded a small number of patients with temporal lobe stroke. This may have lowered the possibility that we might have identified medial temporal lobe structures involved in the group classification. For these reasons, these findings need to be replicated in an independent sample of patients with stroke. Still, the results suggest that thalamic damage, apart from frank thalamic infarction, is a contributing factor in the development of cognitive impairment after ischemic stroke.

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Disclosures
None.

References


