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Gray matter in amnesic mild cognitive impairment: voxel-based morphometry

David Bonekamp^a, Michael A. Yassa^d, Cynthia A. Munro^b, Rena J. Geckle^a, David M. Yousem^a, Peter B. Barker^a, David J. Schretlen^{a,b}, Jason Brandt^{b,c}, and Alena Horská^a

^a The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, Maryland ^b Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, Maryland ^c Department of Neurology, Johns Hopkins University, Baltimore, Maryland ^d Center for Neurobiology of Learning and Memory, Department of Neurobiology and Behavior, University of California, Irvine, California, USA

Abstract

Multiple regression voxel-based morphometry analyses were used to examine the relationship between regional gray matter volumes and neurocognitive performance in 10 patients with amnesic mild cognitive impairment and 20 healthy age-matched controls. Cognitive functioning was assessed with seven standardized neuropsychological tests. Patients with amnesic mild cognitive impairment exhibited impaired cognitive performance (on the Mini Mental State Examination, tests of verbal fluency, verbal and spatial learning and memory, and visual-motor abilities) and reduced gray matter volume in the right temporal pole. Across all participants, better performance on several neuropsychological tests was associated with higher regional gray matter volumes. Voxel-based morphometry provides an operator-unbiased means to investigate volumetric differences, which may be related to impaired neuropsychological functioning.

Keywords

aging; gray matter volume; mild cognitive impairment; neuropsychological assessment; temporal lobe; voxel-based morphometry

Introduction

Mild cognitive impairment, characterized by slight impairment in cognitive functioning but preserved ability to function in daily life, is a transitional state between normal aging and dementia [1]. Criteria for amnesic form of mild cognitive impairment emphasize impaired memory function for age and education, with preserved general cognitive function [1]. Patients with mild cognitive impairment are at increased risk of developing Alzheimer's disease. Alzheimer's disease-related neurodegeneration includes six histopathological stages; the disease process is initially confined to the entorhinal cortex, the transentorhinal

Correspondence to Alena Horská, PhD, The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University, 600 N. Wolfe Street, Park Building, 3rd Floor, Room 367H, Baltimore, MD 21287, USA Tel: +1 410 614 2707; fax: +1 410 502 6076; ahorska@jhmi.edu.

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cortex, and the anterodorsal nucleus of the thalamus and progresses to involve the hippocampal region [2].

Voxel-based morphometry is a neuroimaging tool that provides an operator-unbiased means to investigate volumetric changes [3]. Several studies applied voxel-based morphometry to examine brain tissue volume reduction in mild cognitive impairment [4,5]. Volume reduction detected by voxel-based morphometry techniques in mild cognitive impairment is most notable in the medial temporal lobe, the insula, and the thalamus [4,5]. Patients who converted to Alzheimer's disease had lower baseline gray matter (GM) volumes of the hippocampus, parahippocampal cortex, and lingual and fusiform gyri [6] and volume reduction in the parietal and cingulate cortices [4]. Although previous studies have documented that volumetric changes can be detected in patients with mild cognitive impairment, and may be predictive of progression to Alzheimer's disease, only a limited number of studies focused on the relationship between structural changes and functional impairment. A positive correlation between executive function and the left middle frontal gyrus volume has been observed in patients with mild cognitive impairment [7]. Another study found a negative correlation between scores of Trail Making Test, part A, and gray matter density in the right precuneus in progressive patients with mild cognitive impairment and a positive correlation between delayed wordlist recall and hippocampal gray matter density in patients with stable mild cognitive impairment [8].

The goal of our study was to compare gray matter volumes in a group of patients with amnesic mild cognitive impairment and healthy controls, and evaluate the relationship between regional gray matter volumes and performance on neuropsychological tests. Voxel-based morphometry provided a novel approach to localize anatomical correlates of cognitive impairment that was indicated by impaired performance on neuropsychological tests covering a wide range of cognitive capacities.

Methods

Ten patients with a clinical diagnosis of amnesic mild cognitive impairment (mean age 73.5 ± 5.5 years, five men, age range 65.3–80.3 years) and 20 healthy elderly volunteers (mean age 75.5 ± 4.6 years, 10 men, age range 68.0–86.0 years) were examined. Patients were recruited from the Alzheimer's Disease Research Center. Healthy volunteers were recruited by advertising in the city area. The neurological, psychiatric, and neuropsychological status of all patients and controls was evaluated using standardized instruments and methods. The psychiatric evaluation included administration of the Structured Clinical Interview for *Diagnostic and Statistical Manual*, Fourth Edition, Axis I Disorders (clinical version) [9] and the Clinical Dementia Rating scale [10]. All patients had Clinical Dementia Rating of 0.5 and Mini-Mental State Examination (MMSE) scores within normal limits for age and education [11] (Table 1). Diagnosis of amnesic mild cognitive impairment was based on Petersen's criteria [1], which included a memory complaint, poor memory on testing, otherwise normal cognitive functioning, and no decline in functional ability. Final diagnoses were reached by clinical consensus. Exclusion criteria included abnormal findings on clinical neurological examination (other than mild cognitive impairment criteria for the patient group), head trauma with loss of consciousness, history of previous neurological illness, and general contraindications to an MRI examination. The study was approved by the Johns Hopkins Institutional Review Board and all participants gave written informed consent.

The neuropsychological test battery consisted of seven tests including the MMSE [12]. Verbal Fluency was evaluated based on word list generation with the letters *s* and *p* used in a similar fashion as in the Controlled Oral Word Association Test [12]. Category fluency was

evaluated with ‘animals’ and ‘supermarket items’ as semantic categories [12]. The Hopkins Verbal Learning Test-Revised (HVLT-R) [13] was applied as a word-list learning task that evaluates the sum of total correct responses for initial three learning trials (total recall), the number of items recalled during a fourth trial after a delay (delayed recall), and the difference between the total number of true-positives and false-positives during the final trial of delayed yes/no-recognition (Recognition Discrimination Index). The Hopkins Board [14] was used to assess memory for objects and their locations on a 3 × 3 board. Scores were obtained for the number of trials to criterion, the number of correctly recalled items (delayed recall of items), and locations (delayed recall of locations). The Trail Making Test [12] was used to evaluate psychomotor and information processing speed, sequencing, and visual scanning. Time and number of errors made during tracing of a path along 25 numbers (part A) and accordingly numbers 1–13 with interspersed letters A–L (part B) were recorded. The Beery–Buktenica Developmental Test of visual-motor integration (VMI) [12], assessing constructional praxis, requires the participant to copy a series of line drawings of increasing difficulty. In the Brief Test of Attention [15], participants listened to 10 lists of letters and numbers, and were required to state the count of numbers or letters presented in each list. The numbers of correct responses formed the total score.

MRI was performed on a GE 1.5T MR scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA), using the standard quadrature birdcage head coil. The anatomical images were acquired using a high-resolution coronal three-dimensional T₁-weighted spoiled-gradient-recalled echo in the steady-state sequence with 1.5mm slice thickness, 124 slices, 11.1 ms repetition time, 2.1 ms echo time, 20° flip angle, 240 × 240mm² field-of-view, and a matrix of 256 × 192 zero filled to 256 × 256 for a resulting nominal voxel size of 0.94 × 0.94 × 1.5mm³. The scan time was 4 min 30 s.

Voxel-based morphometry analyses were conducted using an optimized protocol [16] in SPM2 (Wellcome Department of Imaging Neuroscience, University College London, London, UK). MR images were segmented into gray matter, white matter, and cerebrospinal fluid. This involved brain extraction and nonlinear spatial normalization to segmented gray matter and white matter standard template images in standard Talairach space [17]. Normalization was conducted using 10 × 10 × 7 discrete cosine transform basis functions. To further improve the normalization and brain extraction, a second segmentation was performed. The resulting image was modulated with the Jacobian determinant of the deformation field used in the normalization step, to reintroduce information about the volume change into the image. The resulting gray matter segments were smoothed with a three-dimensional Gaussian 8mm full-width at half-maximum kernel [3].

Comparison of neuropsychological test scores between the control and amnesic mild cognitive impairment groups was performed using parametric (Student’s *t*-test) and nonparametric (Mann–Whitney *U* test) tests, depending on the results of the Shapiro–Wilk and Kolmogorov–Smirnov normality tests.

To evaluate the effect of age on a specific neuropsychological test performance, random (mixed) effects general linear model (GLM) analyses with group (amnesic mild cognitive impairment, controls) as fixed factors and age as covariate were constructed, controlling for sex. Dependent variables were the scores of the normally distributed phonemic and semantic categorical Verbal Fluency tests, HVLT-R Total Recall raw scores, VMI raw scores, Trail Making Test (part A) scores, and Brief Test of Attention scores. HVLT-R delayed recall and recognition discrimination and Trail Making Test (part B) scores were not included in the GLM analyses because normality was not confirmed. The homogeneity of variance for all variables was assessed with the Box’s *M*-test, and equal error variances with the Levene’s

test. Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, Illinois, USA).

In the voxel-based morphometry analysis, GLM was used to obtain voxel-wise fit coefficients of the gray matter volume parametric maps. The main voxel-based morphometry analysis was performed using multiple linear regression, with age and group as independent variables, controlling for sex. Age values were converted to Z-scores before they were used in the analyses. Voxel-wise β -coefficients were calculated for gray matter volume differences attributable to age and group. All neuropsychological test scores were modeled in separate voxel-based morphometry analyses using GLM, with age and sex as independent variables. To correct for large number of comparisons, a cluster-based approach was used (i.e. the correction was based on spatial extent and not on the peak height of a cluster) [18]. In all analyses, including group comparisons and regression with neuropsychological test scores, a corrected statistical significance threshold was set to P value less than 0.05.

Results

Demographic information and neuropsychological test scores are reported in Table 1. Statistical analyses of neuropsychological test scores showed significantly lower performance in the amnesic mild cognitive impairment group on five out of seven administered tests: MMSE, Verbal Fluency Test (semantic category only), HLT-R (Total Recall, Delayed Recall, Recognition Discrimination Index), Hopkins Board (Trials to Learning Criterion, Delayed Recall of Items, Delayed Recall of Locations), and VMI (all $P \leq 0.024$).

Voxel-based morphometry analyses revealed a main effect of group. Although several clusters were identified that indicate lower gray matter volumes in the amnesic mild cognitive impairment group compared with controls, only one cluster in the right temporal pole (Brodmann area 38; cluster size=359 voxels, $P < 0.016$, Talairach Coordinates $x=25$, $y=11$, $z=-37$) was significant (See Fig. 1a of Supplemental digital content 1 <http://links.lww.com/WNR/A32>).

There was also a strong negative main effect of age on regional gray matter volumes, detected in the pooled data from both groups. Five significant clusters were detected (Table 2), in the right hippocampus/parahippocampal gyrus (See Fig. 1b of Supplemental digital content 1 <http://links.lww.com/WNR/A32>), left lingual gyrus, and left middle frontal gyrus ($P < 0.05$). There was no significant main effect of sex.

Correlations between neuropsychological test scores and regional gray matter volumes are summarized in Table 3. Better scores on the Trail Making Test (part B) were associated with a higher gray matter volume around the central sulcus and better scores on VMI were associated with a higher gray matter volume in the right superior temporal gyrus and the right middle frontal gyrus (See Fig. 1c of Supplemental digital content 1 <http://links.lww.com/WNR/A32>). Higher scores on the MMSE were associated with a higher gray matter volume in the right middle occipital gyrus. For the Hopkins Board, a significant relationship between the number of trials to learning criterion and gray matter volume in the right hippocampus (See Fig. 1d Supplemental digital content 1 <http://links.lww.com/WNR/A32>) and the left temporal and frontal lobe was detected.

Discussion

In this prospective cross-sectional pilot study, voxel-based morphometry was used to assess gray matter volume differences between patients with amnesic mild cognitive impairment

and age-matched controls, and to examine the relationship between regional gray matter volumes and neuropsychological performance. In patients with amnesic mild cognitive impairment, lower gray matter volume was detected in the right temporal pole. Analyses of data from all participants revealed age-related decreases in gray matter volumes in several regions, most notably in the right hippocampus and the parahippocampal gyri. Better performance on MMSE, Hopkins Board, Trail Making Test (part B), and VMI was associated with higher regional gray matter volumes.

In previous studies, volume reductions detectable with voxel-based morphometry in mild cognitive impairment were observed in the hippocampal and inferolateral temporal regions [4], superior temporal gyri, uncus, posterior cingulate, and adjacent precuneus [19]. Areas of involvement also include the thalamus, the insula [4], and frontal and parietal regions [7,8,20]. In patients with amnesic mild cognitive impairment, inferior and medial temporal lobes [21], frontal and parietal gray matter are affected [20]. Our results confirm earlier findings of gray matter volume reduction in the medial temporal lobe [4], which has a known role in learning and memory and deteriorates early in the course of Alzheimer's disease [22]. The extent of volume reduction in patients with amnesic mild cognitive impairment in our study was less widespread than in a recent study including patients with progressive disease [21]. It is therefore likely that our patients were mostly stable at the time of evaluation and that perhaps widespread structural deficits have not yet manifested. The difference found in the right temporal lobe, and not in the left medial temporal lobe, suggests that there may be laterality to volume loss. Although right laterality in tissue atrophy has been reported [23], the findings are not consistent across studies [24].

Association between neuropsychological test performance and gray matter volume reduction in the temporal neocortex and other cortical areas is also consistent with literature data [25]. In our study, multivariate volumetric analysis, including scores of 12 neuropsychological measures, provided an assessment of the correlations with the observed volumetric changes. The association between the limbic and temporal lobe gray matter volumes and the performances on a test of spatial location learning (Hopkins Board; number of trials to learning criterion) and on a test assessing visual-motor abilities (the Beery VMI) indicates that these tests may be sensitive to isolate early changes underlying the disease process involving gray matter volume reduction. The relationship between impaired performance on the spatial location learning test and gray matter volume in the right parahippocampal gyrus complements a previous report of volume reduction in the right hippocampus-amygdala region in mild cognitive impairment [5]. In our study, a significant relationship between MMSE scores and gray matter volumes in the right middle occipital gyrus was also detected. Although the occipital region has not been documented to be involved in early disease progression of mild cognitive impairment to Alzheimer's disease, a recent pilot FDG PET study in individuals with probable Alzheimer's disease reported an association between the performance on the MMSE drawing task and glucose uptake in several brain regions, including the occipital lobe [26].

Although the patient and control groups differed in neuropsychological performance, volumes of brain regions correlating with the neuropsychological tests were not identical as the areas showing volume group differences. It may be possible that the group comparison was not as sensitive as the correlation analyses (which were performed using data from all participants). Another possible explanation includes modulation of neuropsychological performance involving the medial temporal lobe in patients by changes in other cortical regions (either in connectivity or activity).

Conclusion

A novel technique of assessment of the relationship between neuropsychological test scores and regional gray matter volumes was applied in the elderly, including patients with amnesic mild cognitive impairment. Despite limitations because of a relatively small number of patients, the presented results are consistent with previously published voxel-based morphometry studies and provide essential information on the association between gray matter volumes and cognitive performance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic information and neuropsychological test scores

Group	Controls		Mild cognitive impairment		P value
	Mean	SD	Mean	SD	
Number of participants	20		10		
Number of men/women	10/10		5/5		
Age (years)	75.3	4.8	72.7	5.3	NS
Mini Mental State Examination	28.9	1.2	26.3	2.9	0.003 ^a
Verbal fluency					
Phonemic category	30.0	7.7	27.0	8.8	NS
Semantic category	47.4	10.6	35.8	7.8	0.007 ^a
Hopkins Verbal Learning					
Test-Revised					
Total Recall	25.4	5.1	16.9	6.2	0.001 ^a
Delayed Recall	9.1	1.8	3.3	3.8	0.002 ^b
Recognition Discrimination Index	10.8	1.6	7.1	2.5	0.002 ^b
Hopkins Board					
Trials to Learning Criterion	4.4	2.6	8.8	1.7	<0.001 ^a
Delayed Recall of Items	8.4	0.9	5.8	2.7	0.001 ^b
Delayed Recall of Locations	8.6	0.9	5.4	3.4	0.017 ^b
Trail Making Test					
Part A	47.9	13.2	39.1	14.1	NS
Part B	90.0	30.6	143.1	102.7	NS
Visual Motor Integration	20.1	3.4	16.7	3.8	0.024 ^a
Brief Test of Attention	6.8	2.6	5.8	2.9	NS

Data are presented as means and standard deviations (SD).

Age, phonemic and semantic categorical Verbal Fluency Test scores, and Hopkins Verbal Learning Test-Revised Total Recall raw scores were all normally distributed variables based on the Kolmogorov-Smirnov test and the Shapiro-Wilk tests. The Trail Making Test (part A) and Brief Test of Attention scores were found normally distributed only by the Shapiro-Wilk test and Visual Motor Integration scores were normally distributed only by the Kolmogorov-Smirnov test.

NS, not significant.

^a Statistically significant values, two-tailed Student's *t*-test.

^b Statistically significant values, Mann–Whitney *U* test.

Table 2

Clusters showing a main effect for age

Cluster size	Cluster <i>P</i>	Peak <i>T</i>	Talairach coordinates			Region
			<i>X</i>	<i>Y</i>	<i>Z</i>	
778	0.001	4.47	28	-14	-18	Right hippocampus/parahippocampal gyrus
		3.81	23	-7	-15	Right parahippocampal gyrus
368	0.015	4.87	-15	-82	-14	Left lingual gyrus
272	0.032	4.27	-44	22	31	Left middle frontal gyrus
		4.26	-50	12	31	Left middle frontal gyrus

Data from all participants were used in the voxel-based morphometry analysis.

Table 3

Regions showing a main effect for neuropsychological test scores

Test	Cluster size	Cluster P	Peak T	Talairach coordinates			Region
				X	Y	Z	
MMSE	283	0.029	5.1	35	- 82	7	Right middle occipital gyrus
HB-TTC	268	0.033	4.13	24	- 6	- 13	Right parahippocampal gyrus
	268	0.033	3.71	29	- 14	- 18	Right parahippocampal gyrus
	250	0.039	4.41	- 50	- 30	- 20	Left fusiform gyrus
TMT-B	3183	0.001	8.15	50	- 16	57	Right postcentral gyrus
	3183	0.001	4.09	35	- 12	63	Right precentral gyrus
	369	0.033	5.22	37	12	57	Right middle frontal gyrus
	322	0.044	3.98	46	48	18	Right middle frontal gyrus
VMI	483	0.017	4.36	50	2	1	Right superior temporal gyrus
	365	0.034	4.6	45	31	19	Right middle frontal gyrus

Data from all participants were used in the voxel-based morphometry analyses.

HB-TTC, Hopkins Board-Trials to Learning Criterion; MMSE, Mini Mental State examination; TMT-B, Trail-Making Test-part B; VMI, Beery-Buktenica Developmental Test of Visual Motor Integration.