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Structural MRI discriminates individuals with Mild Cognitive Impairment from age-matched controls: A combined neuropsychological and voxel based morphometry study

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Abstract

Background—Several previous studies have reported that amnesic mild cognitive impairment (aMCI), a significant risk factor for Alzheimer’s disease (AD), is associated with greater atrophy in the medial temporal lobe (MTL) and posterior cingulate gyrus (PCG).

Method—In the present study, we examined the cross-sectional accuracy (i.e., the sensitivity and specificity) of voxel-based morphometry (VBM) in discriminating individuals with MCI (n = 15) from healthy age-matched controls (n = 15). In addition, we also sought to determine whether baseline GM volume predicted aMCI patients that converted to AD from those that did not approximately 2 years after the baseline visit.

Results—MCI patients were found to display significantly less GM volume in several hypothesized regions including the MTL and PCG relative to the age-matched controls ($p < 0.01$). Logistic regression analysis and receiver operating characteristic (ROC) curves for GM volume in the anterior MTL and PCG revealed high discriminative accuracy of 87%. By contrast, baseline GM volume in anterior MTL and PCG did not appear to be sensitive to changes in clinical status at the follow-up visit.

Conclusion—These results suggest that VBM might be useful at characterizing GM volume reductions associated with the diagnosis of aMCI.

Keywords

Mild cognitive impairment; Alzheimer’s disease; Voxel-based morphometry; Hippocampus; Posterior cingulate gyrus; Sensitivity and specificity

1. Introduction

Mild cognitive impairment-amnesic type (aMCI) is a term typically used to describe the earliest stage of Alzheimer’s disease (AD) [1]. Peterson et al. [2] have sought to establish clinical criterion for the diagnosis of aMCI. These criteria include the presence of subjective memory complaints preferably corroborated by an informant, objective episodic memory

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impairment (1.5 standard deviations below age-matched normal subjects), intact activities of daily living, and cognitive/functional status not consistent with the diagnosis of dementia [1]. Using these criterion, the large-scale, multi-center, Alzheimer's Disease Cooperative Study found that 212 of 214 (99%) cases of aMCI eventually met the clinical criteria for possible or probable AD, indicating that the enrollment criteria for aMCI were highly specific [3].

Several recent structural MRI studies using primarily region of interest (ROI) tracing methods have reported that individuals with aMCI display greater atrophy in the medial temporal lobes (MTL) relative to age-matched controls [see 4 for review]. Furthermore, longitudinal MRI studies have found that MTL atrophy was a good predictor of individuals with aMCI who subsequently developed AD from those who did not over a 3–5 year follow-up periods [5–7].

Recent advances in structural MRI image analysis such as voxel-based morphometry (VBM) allow an unbiased mapping of gray matter (GM) volume [8]. The automated VBM procedure has a high degree of reproducibility, and has been previously used to examine GM volume in both AD and aMCI. These studies generally report findings consistent with observations from studies using manual ROI or histopathological methods. For example, Karas et al. [9] found that individuals with aMCI had significantly reduced GM volume in the MTL relative to age-matched controls. Furthermore, AD patients had significantly less GM volume in both posterior cingulate gyrus (PCG) and MTL relative to the aMCI and control groups. However, no differences in GM volume in the PCG were found between the aMCI patients and controls. Together, these results suggest that VBM might be useful at characterizing neuropathological changes associated with the early stages of AD.

In the present study, we used VBM to 1) replicate previous findings of regional GM volume reductions in a group of patients who met the criteria for aMCI, 2) the area under the curve (AUC) of receiver-operating characteristic (ROC) analysis to determine the sensitivity and specificity of VBM at separating aMCI patients from age-matched controls, and 3) determine whether baseline GM volume was associated with longitudinal changes in clinical status in the aMCI patients. The combined use of different ROIs might result in better accuracy than the use of one ROI (e.g., hippocampus) alone. Based on previous studies, we hypothesized that aMCI patients would display reduced GM volume in the MTL, PCG, and temporal/parietal cortices.

2. Methods

2.1. Participants

Fifteen individuals were identified that met the Petersen [1] criteria for aMCI. These individuals were then matched to 15 healthy elderly control participants based on gender, age, and education (see Table 1). Each group consisted of nine men and six women. All subjects received a detailed neuropsychological evaluation examining several cognitive domains. aMCI patients were referred from the several memory disorders clinics at a university-based medical center. The diagnostic criteria for aMCI were those recommended by Petersen [1] including: a) presence of memory complaints by the patient that was preferably corroborated by an informant, b) objective memory impairment defined as performance that was 1.5 SD below the cutoff for normal aging on at least one of four memory measures, c) essentially intact activities of daily living, and d) cognitive and functional status not consistent with a diagnosis of dementia. Prior to inclusion in this study, the aMCI patients were presented to a diagnostic consensus panel for support of the diagnosis. Longitudinal follow-up data (mean follow-up interval = 1.83 ± 0.68 years) were available for 12 aMCI patients (80%). Follow-up data for the majority of the elderly controls was not available because the design of our longitudinal study is to follow individuals meeting the criterion for aMCI.

Subjects that met the clinical criterion for multi-domain or non-amnesic MCI were excluded from the statistical analyses. Additional exclusion criteria for both groups included Hachinski score greater than four, prior neurological disease or neurosurgery, current diagnosis of major psychiatric disorder (including depression), or chronic major medical conditions (e.g., diabetes, poorly controlled hypertension, or cardiac disease). Elderly control participants were recruited from the community, predominantly by advertisement, mailings, and community outreach events. Control participants exhibited normal baseline performance across cognitive domains as assessed by the same battery of neuropsychological measures used to determine cognitive impairment in the aMCI patients (see Table 1).

2.2. Neuropsychological assessment

The aMCI patients and elderly controls received a battery of neuropsychological tests using standardized administration procedures. The memory measures used for the diagnosis of aMCI included long-delay recall and total word recall (trials 1–5) of the Rey Auditory Verbal Learning Test (RAVLT) or long-delay recall and total recall (trials 1–3) of the Brief Visuospatial Memory Test-Revised (BVM-T-R). The complete battery of neuropsychological measures included the following tests: RAVLT, BVM-T-R, Mini-Mental Status Exam (MMSE), Judgement of Line Orientation Test (JLO), Controlled Oral Word Fluency Test (COWAT), Clock Drawing Test, Boston Naming Test (BNT), the Wide Range Achievement Test-3 (WRAT-3) reading subtest, and Trail Making Tests A and B. Between-group differences were examined using two-sample t-tests with a Bonferroni-corrected alpha level set at $p < 0.005$ (i.e., $p < 0.05$ divided by 12 comparisons).

2.3. Anatomic imaging

All participants were situated on the bed of a GE 3.0 Tesla MRI scanner, and foam padding was placed on each side of the head to reduce motion related artifacts. A 3D IR-prepped fast gradient echo pulse sequence was administered to provide high-resolution T1-weighted structural images. In order to obtain whole-brain coverage, imaging parameters were as follows: inversion time = 600 ms, fast gradient echo read-out with TR/TE/flip = 9 ms/1.8 ms/20°; acquisition matrix = $256 \times 192 \times 124$ (axial 256×192 in-plane, interpolated to 256×256); FOV = 240 mm; slice thickness = 1.2 mm (124 slices); ± 16 kHz receiver band-width; acquisition time ~ 7.5 minutes. A neuroradiologist viewed the anatomical images from each participant for structural abnormalities not consistent with the subject diagnosis and/or requiring clinical follow-up. The T1-weighted images were then used for the VBM analyses.

2.4. Voxel-based morphometry processing steps & statistical analysis

Analysis of the T1 anatomical images and the subsequent segmentation of these images into GM, white matter (WM), and cerebrospinal fluid (CSF) were performed with the VBM approach described by Good et al. [see also 8,10] using Statistical Parametric Mapping (SPM2) software (<http://www.fil.ion.ucl.ac.uk/spm>).

2.4.1. Template creation—We created customized GM templates by averaging together the T1-weighted anatomical scans of the controls and MCI patients. First, all images were coregistered to the SPM2 T1-weighted template and then partitioned into GM, white matter (WM), and cerebrospinal fluid (CSF) images. Second, the GM images were normalized to the SPM2 GM template using affine only transformations. The normalization parameters obtained for each subject were then reapplied to the original anatomical images. Third, these normalized images were segmented and extracted, and the GM, WM, and CSF images were averaged across the subjects. Finally, Gaussian smoothing (isotropic 8-mm full-width-at-half-maximum) was applied to the mean images to obtain the customized whole-brain template and GM prior probability images that were subsequently used for the VBM analyses.

2.4.2. Single-subject, preprocessing steps—The original anatomical image was segmented into GM, WM, and CSF images, and the GM images were normalized to the custom GM template with a 15 parameter fit. The normalization parameters were re-applied to the original image that was re-sampled using B-splines interpolation to a voxel size of 2 mm³. The normalized brain image was then segmented and the resulting GM images were modulated using the Jacobian values obtained from the spatial normalization in order to preserve GM volume. In the final step, the modulated images were smoothed using a 12-mm isotropic Gaussian kernel.

2.5. Data analysis

2.5.1. VBM group analysis—Smoothed GM images were entered into a random-effects group analysis using the general linear model to compare differences in GM volume between the age-matched control group and the aMCI group. We used an ANCOVA design with total intracranial volume (TICV) as a nuisance variable. Since previous VBM studies in aMCI and AD patients have reported reduced GM volume in the MTL, PCG, and temporal/parietal cortices [e.g., 9, e.g., 11, 12], we restricted our analyses to these regions of interest (ROI) using the Wake Forest University Pick Atlas toolbox [13] within SPM2. Due to the relatively small sample size and the a-priori ROI approach used, between group differences were examined using an alpha level set at $p < 0.01$ (uncorrected for multiple comparisons). In a second step, we used a voxel-level, FDR-corrected threshold ($p = 0.05$) to further evaluate the presence of significant differences in GM volume in unhypothesized brain regions [see also 12].

2.5.2. Logistic regression and ROC analysis—The area under the curve (AUC) for receiver operating characteristic (ROC) analysis was computed to determine whether VBM could accurately discriminate aMCI patients from age-matched controls. ROC curve analysis is frequently used as an indicator of the ability of a classification test to discriminate individuals with and without a disease [14]. The ROC curve examines the true-positive rate (or sensitivity) relative to the false-positive rate (or 1-specificity). AUC values range from 0.50 (test is no better than chance) to 1 (test is always accurate). The greater the accuracy of the test the closer the ROC plot is to the upper left corner.

The a-priori defined ROIs for the VBM group analysis included the PCG and MTL. We then used the volume of interest (VOI) option in SPM2 to extract adjusted GM volume values from a 2 mm radius sphere (corresponding to 7 contiguous voxels with a voxel size = 2 mm³ for a total volume of 56 mm³) centered on the local maxima within the PCG and MTL ROIs. The GM values were used in a logistic regression analyses to assess whether reduced PCG or MTL GM volume were significant predictors of the baseline diagnosis of aMCI obtained from the neuropsychological data. Results were considered significant at an alpha level of $p < 0.05$. Statistical analyses were computed with SPSS (version 12).

3. Results

3.1. Neuropsychological and demographic data

There were no significant baseline differences between the two groups in terms of age or education ($p > 0.50$). However, chi square analysis for APOE genotype revealed a significantly greater percentage of APOE ε4 carriers in the aMCI group relative to the control group ($\chi^2 = 19.3$, $p < 0.01$). Furthermore, aMCI patients were significantly impaired relative to the age-matched control group for the MMSE, RAVLT long delay recall and total word recall (trials 1–5), BVMt long delay recall and total recall (trials 1–3), and Trails Making Test B. Although the performance of the aMCI patients on Trail Making Test B was within age-adjusted, normal limits. There were no significant differences between the two groups after correction for multiple comparisons for the other neuropsychological test measures (see Table 1).

3.2. VBM data - group comparison

The VBM group analysis revealed several areas where local GM volume was reduced in the aMCI group relative to the control group (Fig. 1, Table 2). We found that aMCI patients displayed greater atrophy relative to the control group in hypothesized regions including left PCG, left anterior MTL (AMTL), left hippocampus/parahippocampal gyrus (HPC/PHG), and the right temporal (middle and inferior) gyrus. The follow-up whole-brain analysis did not reveal any additional significant regions of reduced GM volume after correction for multiple comparisons. Given the large range of age in both the aMCI and age-matched groups, the analysis was redone with age and TICV as nuisance variables and a similar pattern of reduced GM volume was observed. In contrast, there were no regions in which the aMCI group displayed significantly greater GM volume relative to the control group even at the more liberal threshold of $p < 0.05$ (uncorrected). These results replicate the findings of previous studies that have demonstrated GM volume reductions in the PCG and MTL of individuals with aMCI.

3.3. Logistic Regression and ROC curve analysis

The logistic regression model testing the contribution of AMTL, PCG, and HPC/PHG GM VOIs to discriminate MCI patients from age-matched controls revealed that all three values were independent predictors of group assignment ($B = -4.02$, $SE = 1.61$, $p = 0.01$ for the AMTL VOI; $B = -7.61$, $SE = 3.0$, $p = 0.01$ for PCG VOI; and $B = -1.93$, $SE = 0.83$, $p = 0.02$ for the HPC/PHG VOI). GM volume in the AMTL was the best predictor of group assignment (accuracy = 83%) with a sensitivity and specificity of 87% and 80%, respectively. The AUC for the ROC curve analysis was 0.88, 95% C.I., 0.74–1.01. The accuracy of the aMCI diagnosis for the PCG VOI was 73% (sensitivity and specificity were both 73%). The AUC for the ROC curve analysis within the PCG VOI was 0.81, 95% C.I., 0.66–0.97. In contrast, the GM volume in the HPC/PHG cluster was much less predictive of the MCI diagnosis with 60% accuracy, 67% sensitivity, 53% specificity, and an AUC for the ROC curve analysis of 0.79 (95% C.I., 0.63–0.95). When both the AMTL and PCC GM values were included in the analysis, the overall accuracy of discrimination improved to 87% (AUC = 0.88) (see Fig. 2).

3.5. Longitudinal follow-up

Longitudinal follow-up neuropsychological and clinical data were available for 12 of 15 (80%) aMCI patients that received baseline MRI scans. Of the 12 aMCI patients, 3 had converted to AD based on NINCDS-ADRDA criterion and 2 displayed a worsening in function, but still did not meet the clinical criterion for AD. The cognitive status of the remaining 7 aMCI patients remained relatively stable over the follow-up period.

A second logistic regression within the aMCI patient group with clinical status at the follow-up visit (i.e., convert to AD versus stable aMCI) was done to determine if baseline GM volume at each of the 3 VOIs used in the baseline logistic regression were predictive of the conversion of aMCI to AD. The GM volume values for each of the 3 VOIs and the clinical status at the follow-up visit for each of the aMCI patients can be seen in Fig. 3. The GM volume values for the vast majority of the aMCI patients was below the mean of the control group at all 3 VOIs (14/15 for AMTL and HPC/PHG VOIs and 13/15 for the PCG VOI) (see Fig. 3). The GM volume of subjects that declined from aMCI to AD were each below the mean of the elderly controls, but were not consistently less than the baseline GM volume of the aMCI patients that were stable at follow-up. This was confirmed by our failure to demonstrate that baseline GM volume from the 3 VOIs was able to discriminate (p 's > 0.35) between aMCI patients that remained stable versus those that converted to AD.

4. Discussion

The present study used VBM to: 1) examine regional differences in GM volume in individuals with aMCI relative to age-matched controls, 2) determine the sensitivity and specificity of VBM-based measures at discriminating between aMCI patients and age-matched controls, and 3) to determine whether baseline GM volume predicted those aMCI patients that declined to AD at the follow-up visit.

We found that aMCI patients displayed reduced GM volume relative to the age-matched controls in several brain regions previously reported to display volumetric declines in AD and aMCI. aMCI patients displayed reduced GM volume in the MTL (including hippocampus, amygdala, and fusiform gyrus), the PCG, and the right middle and inferior temporal gyri. The left AMTL was found to display the most significant reductions in GM volume in our group of aMCI patients.

These findings are consistent with previous VBM studies of aMCI and AD, which have generally found the most significant GM volume reductions in the MTL. For example, Karas et al. [9] reported the most significant reductions in GM volume in the hippocampus, amygdala, and middle temporal gyrus of both MCI and AD patients [see also 11,15]. These findings are also consistent with ROI studies of MTL volume. Bottino et al. [9] reported that AD patients had significant bilateral reductions in GM volume in the hippocampus, amygdala, and parahippocampal gyrus relative to MCI patients and healthy, control subjects. MCI patients were found to display significant, left-lateralized reductions in GM volume in these same regions relative to controls. Similar findings have been reported by several previous studies [11,12,16–19].

We also found that individuals with aMCI displayed reduced GM volume in the PCG. These findings are also consistent with recent ROI tracing studies, which have also reported volume reductions in the PCG of AD patients [20,21]. Previous VBM studies in aMCI have reported conflicting findings regarding GM volume reductions in this region. For example, Chetelat et al. [11] reported reduced GM volume in the PCG of aMCI patients, whereas Karas et al. [9] did not find any differences between aMCI patients and controls [see also 15]. However, AD patients were found to have significantly less GM volume in the MTL, PCG and parietal association cortices relative to aMCI patients. The exact reason for these conflicting findings is not known, and might be due to differences in the diagnostic criterion used for aMCI [22] or other technical issues (e.g., different field strength MRI scanners or differences in the statistical thresholds employed). Reduced GM volume in the PCG might also suggest that some of the aMCI patients in the present study were closer to AD than others (in fact 3 aMCI patients were found to have converted to AD at the follow-up visit). This would also be consistent with the findings that performance on non-memory measures (i.e., Trail Making Test B) was also significantly poorer in the aMCI group.

In the present study, GM volume in the AMTL and PCG VOIs were found to be better independent predictors of group assignment than GM volume in the HPC/PHG VOI. When both AMTL and PCG GM VOIs were entered into the logistic regression model, accuracy of correctly classifying individuals as aMCI versus controls improved to 87%. These findings are consistent with Bottino et al. [23], who correctly classified 88% of the AD patients relative to controls, 82% of AD patients relative to aMCI subjects, and 81% of the MCI subjects relative to controls when manually-traced ROIs of the amygdala, hippocampus and para-hippocampal gyrus were included together in the regression model. Testa et al. [24] used both manual ROI and automated VBM measures of MTL GM volume in AD, and found that VBM was superior to the ROI based method at distinguishing between AD patients and age-matched controls [see also 17,18].

Previous studies that have examined the diagnostic accuracy of only hippocampal GM volume measurements at classifying aMCI patients versus controls have reported poor diagnostic accuracy (i.e., 68 – 73%) [see 4 for review], consistent with the findings of the present study. The poor accuracy observed using hippocampal volumetric measurements may reflect heterogeneity in episodic memory impairment used to diagnose MCI [4] or the presence of reduced hippocampal volume in the control group used for comparison. It is also possible that the better discriminative ability of the AMTL might be due to the fact that the AMTL VOI was more likely to be in a general block of tissue in the MTL than the HPC/PHG VOI, possibly due to variability in the size/shape of MTL subregions associated with normal aging or aMCI. This variability in regional brain morphology might therefore reduce the accuracy of spatial normalization thereby reducing the power of VBM to detect group differences. For example, Mosconi et al. [25] found that only 3% of the hippocampus displayed 100% overlap using voxel-based methods similar to the present study. In any case, the baseline HPC/PHG VOI obtained from the VBM analysis in the present study did not appear to adequately distinguish aMCI subjects from normal controls. Therefore, the results of the present study are consistent with previous findings [23], indicating that the combined use of regional ROIs is more sensitive than a single ROI to the clinical diagnosis of aMCI.

Longitudinal studies have reported that reductions in hippocampal volume over time were predictive of those MCI patients that converted to AD from those that did not [see 4 for review]. More recently, Chetelat et al. [26] conducted a longitudinal VBM study of GM volume comparing MCI patients that converted to AD versus those that did not. These authors reported that over an 18-month follow-up period, both AD converters and non-converters displayed GM loss in temporal and parahippocampal gyri, orbitofrontal and inferior parietal areas, and the left thalamus. In contrast, AD converters displayed significantly greater GM loss relative to non-converters in the hippocampus, inferior and middle temporal gyrus, posterior cingulate, and precuneus during the follow-up period. Together, these results suggest that structural and functional changes in both hippocampus and PCG are predictive of the conversion from MCI to AD.

This study has several limitations that reduce the generalizability of the present findings. First, the brain regions used for the sensitivity and specificity analysis were biased by our a-priori knowledge of brain regions in which our group of aMCI patients displayed significantly less GM volume. Future studies will be able to examine sensitivity and specificity of the clinical diagnosis of aMCI, and whether regional GM volume can predict conversion to AD with the VOIs used in this study or those reported by others [17,18,24,27], preferably with larger sample sizes. Second, despite our rigorous inclusion and exclusion criterion for both groups, it is quite possible that some of the aMCI patients were not in the early stages of AD, since a small percentage of individuals diagnosed with possible or probable AD are found on autopsy to have other neurodegenerative dementias [e.g., 28]. Therefore, it is possible that some of the aMCI patients in our study were not in the early stages of AD. Longitudinal VBM studies similar to the study by Chetelat et al. [26] would be useful in determining whether or not aMCI patients that convert to AD display a different pattern of longitudinal decline in regional GM volume relative to aMCI patients that do not rapidly convert to AD. Despite these limitations, the results of the present study indicate that the combined use of GM volume in the AMTL and PCG had better discriminative ability for aMCI than either region alone.

In summary, the present study found that aMCI patients displayed reduced GM volume in several regions such as PCG, MTL, and medial and inferior temporal gyri previously reported to display volumetric declines in aMCI and/or AD. These findings are consistent with previous histopathological and MRI based ROI studies. Logistic regression and ROC curve analysis revealed that GM volume from VOIs in the AMTL and PCG were better predictors of group assignment, and the combined use of AMTL and PCG VOIs produced greater accuracy (87%)

than either measure alone. However, baseline GM volume in aMCI patients was not found to be a significant predictor of individuals with aMCI who subsequently developed AD versus those that did not at least over the 2-year follow-up period used in the present study.

More longitudinal studies similar to the present study that combine neuropsychological assessment with structural MRI to examine the time course of pathological changes in PCG and MTL are needed to determine the relationship between structural and cognitive changes in AD. Along with several previous VBM studies, our results suggest that VBM might provide a relatively simple tool for staging the progressive structural changes associated with the AD disease process in vivo.

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References

1. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256:183–194. [PubMed: 15324362]
2. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. *Arch Neurol* 2001;58:1985–1992. [PubMed: 11735772]
3. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005;352:2379–2388. [PubMed: 15829527]
4. Chetelat G, Baron JC. Early diagnosis of Alzheimer's disease: contribution of structural neuroimaging. *Neuroimage* 2003;18:525–541. [PubMed: 12595205]
5. Jack CR Jr, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology* 1999;52:1397–1403. [PubMed: 10227624]
6. Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology* 2000;55:484–489. [PubMed: 10953178]
7. Jack CR Jr, Shiung MM, Gunter JL, O'Brien PC, Weigand SD, Knopman DS, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology* 2004;62:591–600. [PubMed: 14981176]
8. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage* 2000;11:805–821. [PubMed: 10860804]
9. Karas GB, Scheltens P, Rombouts SA, Visser PJ, van Schijndel RA, Fox NC, et al. Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 2004;23:708–716. [PubMed: 15488420]
10. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001;14:21–36. [PubMed: 11525331]
11. Chetelat G, Desgranges B, De La Sayette V, Viader F, Eustache F, Baron JC. Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. *Neuroreport* 2002;13:1939–1943. [PubMed: 12395096]
12. Remy F, Mirrashed F, Campbell B, Richter W. Verbal episodic memory impairment in Alzheimer's disease: a combined structural and functional MRI study. *Neuroimage* 2005;25:253–266. [PubMed: 15734360]
13. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003;19:1233–1239. [PubMed: 12880848]

14. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29–36. [PubMed: 7063747]
15. Pennanen C, Testa C, Laakso MP, Hallikainen M, Helkala EL, Hanninen T, et al. A voxel based morphometry study on mild cognitive impairment. *J Neurol Neurosurg Psychiatry* 2005;76:11–14. [PubMed: 15607988]
16. Chetelat G, Desgranges B, de la Sayette V, Viader F, Berkouk K, Landeau B, et al. Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. *Brain* 2003;126:1955–1967. [PubMed: 12821520]
17. Hirata Y, Matsuda H, Nemoto K, Ohnishi T, Hirao K, Yamashita F, et al. Voxel-based morphometry to discriminate early Alzheimer's disease from controls. *Neurosci Lett* 2005;382:269–274. [PubMed: 15925102]
18. Ishii K, Kawachi T, Sasaki H, Kono AK, Fukuda T, Kojima Y, et al. Voxel-based morphometric comparison between early- and late-onset mild Alzheimer's disease and assessment of diagnostic performance of z score images. *AJNR Am J Neuroradiol* 2005;26:333–340. [PubMed: 15709131]
19. Karas GB, Burton EJ, Rombouts SA, van Schijndel RA, O'Brien JT, Scheltens P, et al. A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. *Neuroimage* 2003;18:895–907. [PubMed: 12725765]
20. Barnes J, Godbolt AK, Frost C, Boyes RG, Jones BF, Scallan RI, et al. Atrophy rates of the cingulate gyrus and hippocampus in AD and FTL. *Neurobiol Aging*. 2006
21. Jones BF, Barnes J, Uylings HB, Fox NC, Frost C, Witter MP, et al. Differential Regional Atrophy of the Cingulate Gyrus in Alzheimer Disease: A Volumetric MRI Study. *Cereb Cortex*. 2006
22. Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol* 2005;62:1160–1163. [PubMed: 16009779]discussion 67
23. Bottino CM, Castro CC, Gomes RL, Buchpiguel CA, Marchetti RL, Neto MR. Volumetric MRI measurements can differentiate Alzheimer's disease, mild cognitive impairment, and normal aging. *Int Psychogeriatr* 2002;14:59–72. [PubMed: 12094908]
24. Testa C, Laakso MP, Sabattoli F, Rossi R, Beltramello A, Soininen H, et al. A comparison between the accuracy of voxel-based morphometry and hippocampal volumetry in Alzheimer's disease. *J Magn Reson Imaging* 2004;19:274–282. [PubMed: 14994294]
25. Mosconi L, Tsui WH, De Santi S, Li J, Rusinek H, Convit A, et al. Reduced hippocampal metabolism in MCI and AD: automated FDG-PET image analysis. *Neurology* 2005;64:1860–1867. [PubMed: 15955934]
26. Chetelat G, Landeau B, Eustache F, Mezenge F, Viader F, de la Sayette V, et al. Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: A longitudinal MRI study. *Neuroimage*. 2005
27. Kawachi T, Ishii K, Sakamoto S, Sasaki M, Mori T, Yamashita F, et al. Comparison of the diagnostic performance of FDG-PET and VBM-MRI in very mild Alzheimer's disease. *Eur J Nucl Med Mol Imaging*. 2006
28. Jobst KA, Barnetson LP, Shepstone BJ. Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and Apo E4 in medial temporal lobe dementias. *Oxford Project to Investigate Memory and Aging. Int Psychogeriatr* 1998;10:271–302. [PubMed: 9785148]

Fig. 1.

Regions of greater GM volume in controls relative to aMCI patients. Statistical parametric maps of the VBM analysis representing regions in which age-matched control subjects displayed greater GM volume relative to individuals with aMCI at a threshold of $p < 0.01$ (uncorrected) rendered on the customized GM template used in the VBM pre-processing steps. The left side of the image corresponds to left, and the right side of the image corresponds to the right.

Fig. 2. baseline ROC curve analysis Receiver operating characteristics (ROC) curve of the VBM based AMTL and PCG GM volume measures to separate 15 aMCI patients from 15 controls.

Fig. 3.

Plot of baseline GM volume for the aMCI and elderly control groups. Baseline GM volume from the AMTL, HPC/PHG, and PCG VOIs used for the ROC curve analysis with the clinical status at follow-up for aMCI patients and elderly controls with follow-up data. The x = control group, o = stable aMCI at follow-up visit, Δ = aMCI conversion to AD, + = follow-up clinical status unknown.

Table 1

Demographic and neuropsychological data

	Controls		MCI	
	Mean	SD	Mean	SD
Age (years)	73.6	7.1	73.3	6.72
Education (years)	16.7	2.5	16.3	2.81
Gender Ratio: Female / Male	6/9		6/9	
% APOE e4 carriers *	17%		54%	
MMSE †	29.7	0.5	27.8	1.8
RAVLT total recall trials 1–5 †	46.8	6.5	30.5	5.2
RAVLT long delay recall †	8.9	1.8	1.9	1.9
BVMT total recall trials 1–3 †	23.5	8.0	12.8	5.3
BVMT long delay recall †	9.3	1.8	4.3	2.8
Boston Naming Test	57	3.2	55.7	3.6
COWAT adjusted raw score	46.5	8.9	37.5	9.7
Clock Drawing Test	9.6	1.3	9.4	0.5
JLO Test	25.7	3.01	25.7	3.03
Trail Making Test A (sec)	33.7	7.6	42.2	18.6
Trail Making Test B (sec) ‡	65.9	15.7	92.8	22.5
WRAT-3 reading subtest – Standard Score	118.7	19.7	110.3	7.8

Note: Unless otherwise indicated, all data represent raw scores and are presented as mean (SD).

MMSE =Mini Mental Status Exam, BVMT =Brief Visual Memory Test, COWAT =Controlled Oral Word Fluency Test, JLO = Judgement of Line Orientation Test, RAVLT = Rey Auditory Verbal Learning Test, BNT = Boston Naming Test, WRAT = Wide Range Achievement Test-3. See text for further discussion of test measures.

* significant difference ($p < .01$)

† significant difference ($p < 0.0001$)

‡ significant difference ($p < 0.001$).

Table 2
Montreal Neurological Institute (MNI) coordinates for the VBM analyses (k =cluster size)

Region (k)	MNI coordinates			Peak T value	P uncorrected
	x	y	z		
<i>VBM - Group Analysis Controls > MCI</i>					
L Anterior MTL (157)	-14	6	-22	4.07	<0.0001
L PCG (99)	-18	-28	36	3.26	0.001
L Fusiform Gyrus (127)	-32	-24	-32	2.93	0.003
- L HPC/PHG	-38	-12	-26	2.80	0.005
R Inferior Temporal Gyrus (39)	24	10	-26	2.95	0.003
R Middle Temporal Gyrus (20)s	36	2	-24	2.86	0.004