Patterns of Atrophy Differ Among Specific Subtypes of Mild Cognitive Impairment

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Background: In most patients, mild cognitive impairment (MCI) represents the clinically evident prodromal phase of dementia. This is most well established in amnestic MCI, which is most commonly a precursor to Alzheimer disease (AD). It follows, however, that subjects with MCI who have impairment in nonmemory domains may progress to non-AD degenerative dementias.

Objective: To investigate patterns of cerebral atrophy associated with specific subtypes of MCI.

Design: Case-control study.

Setting: Community-based sample at a tertiary referral center.

Patients: One hundred forty-five subjects with MCI and 145 age- and sex-matched cognitively normal control subjects. Mild cognitive impairment was classified as amnestic, single cognitive domain; amnestic, multiple domain; nonamnestic, single domain; and nonamnestic, multiple domain. Subjects with nonamnestic single-domain MCI were classified into language, attention/executive, and visuospatial subgroups on the basis of specific cognitive impairment.

Main Outcome Measure: Patterns of gray matter loss in the MCI groups compared with control subjects, assessed using voxel-based morphometry.

Results: Subjects in the amnestic single- and multiple-domain groups showed loss in the medial and inferior temporal lobes compared with control subjects, and those in the multiple-domain group also had involvement of the posterior temporal lobe, parietal association cortex, and posterior cingulate. Subjects in the nonamnestic single-domain group with language impairment showed loss in the left anterior inferior temporal lobe. The group with attention/executive deficits showed loss in the basal forebrain and hypothalamus. No coherent patterns of loss were observed in the other subgroups.

Conclusions: The pattern of atrophy in the amnestic MCI groups is consistent with the concept that MCI in most of these subjects represents prodromal AD. However, the varying patterns in the language and attention/executive subgroups suggest that these subjects may have a different underlying disorder.

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nonamnestic multiple-domain MCI (naMCI-MD), the subtype associated with impairment in 2 or more nonmemory domains. This 4-group classification scheme proposed in 2003 has been adopted by the National Institute on Aging Alzheimer's Disease Centers Program for the Uniform Data Set. It is also being used to classify subjects for the Alzheimer's Disease Neuroimaging Initiative. Although this Initiative uses the 4-group scheme for MCI classification, only subjects with aMCI are enrolled in the study. In all previous imaging studies published from the Mayo Clinic, only subjects with aMCI were included in the study analysis. In the current study, however, we analyzed patterns of gray matter atrophy in subjects in all 4 possible MCI groups.

The analysis was conducted at 2 levels: the subjects were first categorized into the 4 MCI subtype groups (ie, aMCI-SD, aMCI-MD, naMCI-SD, and naMCI-MD); then the subjects in the naMCI-SD group were further classified according to whether their cognitive impairment was language, attention/executive, or visuospatial. Whereas all or nearly all previous imaging reports have focused on aMCI, early estimates indicate that as many as one fourth of subjects with MCI may have the nonamnestic variety. By providing clinical imaging correlations for each MCI subtype, we hoped to clarify the overall conceptual construct of MCI.

SUBJECTS

The Mayo Clinic Alzheimer Disease Research Center and Alzheimer Disease Patient Registry databases were used to identify all subjects who had a clinical diagnosis of MCI and had undergone volumetric magnetic resonance imaging (MRI) within 4 months of the diagnosis. All subjects fulfilled clinical criteria for cognitive impairment and were examined and diagnosed by experienced behavioral neurologists (R.C.P., D.S.K., and R.F.B.). In all cases, the diagnosis was made on clinical grounds without reference to MRI. For this study, to assess the anatomical correlations of the various subtypes of MCI, a subset of our previous clinical cohorts was defined a priori on the basis of neuropsychological criteria (see “Neurological Data” and “Subject Classification”). Written informed consent was obtained from all subjects. The clinical history and MRIs were reviewed in all cases. Subjects with structural abnormalities that could produce cognitive impairment or who had undergone treatments or had concurrent illnesses interfering with cognitive function either at baseline or during follow-up were not included in this study. Magnetic resonance images were rejected if they were of poor quality. The first MRI confirming a clinical diagnosis of MCI was selected for analysis.

All subjects with MCI who were included in the analysis were age- and sex-matched to a control subject. The date and year that MRI was performed were also matched in an attempt to control for any temporal fluctuations associated with different scanner platform versions. All control subjects were prospectively recruited into the Mayo Clinic Alzheimer Disease Research Center or the Alzheimer Disease Patient Registry and were identified from these databases.

Follow-up information was available for some subjects. The number of subjects in each group who have since received a clinical diagnosis of dementia was recorded, along with the specific dementia diagnosis and the duration of follow-up.

NEUROPSYCHOLOGICAL DATA

Neuropsychological data were available for all subjects within 4 months of the MRI date. Neuropsychological tests were classified into memory, language, attention/executive, and visuospatial domains, as validated and implemented in a recent large MCI treatment trial. The memory tests included in this study were the Wechsler Memory Scale (WMS)–Revised, WMS Logical Memory subtest, WMS-Revised Visual Reproduction subtest, Rey Auditory Verbal Learning Test, and the Free and Cued Selective Reminding Test total recall score. The language tests included the Boston Naming Test, and the Controlled Oral Word Association Test. The attention/executive tests included the Trail Making Test, parts A and B, and the Digit Symbol and Digit Span subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS-R) or the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III). The visuospatial tests included the Picture Completion, Block Design, and Object Assembly subtests of the WAIS-R or WAIS-III. All tests were administered by experienced psychometrists and supervised by clinical neuropsychologists (R.J.I. and G.E.S.). Mayo Older American Normative Studies (MOANS) age-adjusted scaled scores were used for all neuropsychological variables except those derived from the WAIS-III. The MOANS scores are constructed to have a mean of 10 and SD of 3 in cognitively healthy participants. Early participants in this study had received the WAIS-R; later subjects received the WAIS-III.

SUBJECT CLASSIFICATION

A mean MOANS score was created for each domain. This involved taking the mean MOANS scores of all tests in the language, attention/executive, and visuospatial domains. In the memory domain, a mean was calculated using the percent retention score from the Logical Memory and Visual Reproduction subtests, the short-term and long-term Auditory Verbal Learning Test, and the Free and Cued Selective Reminding Test total learning score. To be classified as impaired in a domain, a subject had to have a mean MOANS score of 6 or lower, reflecting a score of 1.3 SD below the control mean of 10, and below the 10th percentile. If the mean MOANS score was 7 or higher, the domain was classified as unimpaired.

Subjects were first classified into 1 of 4 MCI categories: aMCI-SD (only memory domain impaired), aMCI-MD (memory plus 1 or more other domains impaired), naMCI-SD (1 nonmemory domain impaired), or naMCI-MD (more than 1 nonmemory domain impaired). We used a subset of all subjects with clinically defined MCI, as follows. Of 143 subjects with MCI who had usable MRIs, 88 subjects were classified as having aMCI-SD, 25 as having aMCI-MD, 25 as having naMCI-SD, and 7 as having naMCI-MD. The 25 subjects with naMCI-SD were then subdivided into groups on the basis of the domain in which impairment was observed. Ten of these subjects had language impairment, 9 had attention/executive impairment, and 6 had visuospatial impairment.

IMAGE ANALYSIS

In all subjects, a T1-weighted volumetric MRI was acquired at 1.5T (22 × 16.5-cm field of view, 25° flip angle, and 124 contiguous 1.6-mm-thick coronal sections). An optimized method of voxel-based morphometry (VBM) was applied, implemented using SPM2 software (Statistical Parametric Mapping, version 2; Wellcome Department of Imaging Neuroscience, University College London, London, United Kingdom). To reduce any potential normalization bias across the disease groups,
customized templates and prior probability maps were created for all study subjects including those with MCI and control subjects. To create the customized template and prior probability maps, all images were registered to the Montreal Neurologic Institute (MNI) template using a 12 df affine transformation and segmented into gray matter, white matter, and cerebrospinal fluid and smoothed using an 8-mm full width at half maximum smoothing kernel. The gray matter images were normalized to the MNI gray matter template and segmented again using the MNI prior probability maps. Average images were created of the whole head, and the images were segmented using the MNI prior probability maps. All images were then registered to the customized whole brain template using a 12 df affine transformation and segmented using the customized prior probability maps. The gray matter images were normalized to the original whole head, and the images were segmented using the MNI prior probability maps. Average images were created of the whole head, gray matter, white matter, and cerebrospinal fluid and smoothed using an 8-mm full width at half maximum smoothing kernel. All images were then registered to the customized whole brain template using a 12 df affine transformation and segmented using the customized prior probability maps. The gray matter images were normalized to the custom gray matter prior probability maps using a nonlinear discrete cosine transformation. The normalization parameters were then applied to the original whole head, and the images were segmented again using the customized prior probability maps. All images were modulated and smoothed with an 8-mm full width at half maximum smoothing kernel. In addition, a reinitialization routine was implemented, as previously described.

Gray matter differences between each MCI subgroup and the entire control group (n = 145) were assessed at an uncorrected statistical threshold (P < .001) and after correction for multiple comparisons using the false discovery rate (P < .01). Pairwise f tests showed that the aMCI-MD and naMCI-MD groups were significantly different from control groups (P = .002 for aMCI-MD; P = .004 for naMCI-MD), subjects with aMCI-SD (P = .001 for aMCI-MD and naMCI-MD), and subjects with naMCI-SD (P = .007 for aMCI-MD; P = .005 for naMCI-MD). All differences were significant at P < .05 after correction for multiple comparisons.

Significant differences across control groups, aMCI-SD, aMCI-MD, naMCI-SD, and naMCI-MD groups with the Fisher exact test because of some sparse cell counts.

Nonparametric Kruskal-Wallis tests were used to compare Mini-Mental State Examination19 and Mattis Dementia Rating Scale (DRS)20 scores among the MCI groups, with post hoc pairwise comparisons performed using the Wilcoxon rank sum test. The control group was excluded from the Mini-Mental State Examination and DRS analyses because control subjects, by definition, had normal cognition. Within-domain composite MOANS scores were compared across the naMCI-MD subgroups using the Kruskal-Wallis test, with post hoc pairwise comparisons performed using the Wilcoxon rank sum test. All analyses were performed using the statistical software environment R (version 2.2.1; R Development Core Team [2006], R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

SUBJECT DEMOGRAPHIC DATA

Demographic data for the control and MCI groups are given Table 1. There was no statistical difference in age or sex ratio across the control and MCI subgroups. However, both the aMCI-MD and naMCI-MD groups had fewer years of education than any of the other groups.
There were differences in the frequency of APOE ε4 carriers across the MCI subgroups (P < .01), with rates ranging from 14% in the naMCI-MD group to 60% in the aMCI-SD group. There was no difference in Mini-Mental State Examination scores across the MCI groups (P = .19). There were highly significant differences in average DRS scores across the MCI groups (P < .001); using pairwise comparisons, the aMCI-MD group had lower DRS scores than the aMCI-SD (P < .001) and naMCI-MD groups (P = .03), and the naMCI-MD group had lower DRS scores than the naMCI-SD group (P = .009). The follow-up data for all groups are given in Table 2 and Table 3. Of the subjects in the aMCI-SD group who progressed to dementia, most had a diagnosis of AD, whereas a lower percentage of subjects in the naMCI-SD, naMCI-MD, and aMCI-MD groups progressed to a diagnosis of AD. Although many subjects with single-domain impairments in attention and language progressed to AD, some demonstrated progression to other dementias. For example, 2 subjects with naMCI-SD with attention impairment progressed to dementia with Lewy bodies, and 1 subject with language impairment progressed to frontotemporal dementia.

**IMAGE ANALYSIS**

**aMCI-SD Group**

The pattern of gray matter loss in the aMCI-SD group compared with the control group focused on the medial...
and inferior temporal lobes, including the hippocampus, amygdala, entorhinal cortex, and parahippocampal gyrus \( (P < .001, \text{uncorrected for multiple comparisons; Figure 1A}) \). Loss was bilateral but slightly greater on the left. The parietal association neocortex and midbrain were also involved to a lesser extent \( (P < .001, \text{uncorrected for multiple comparisons; Figure 1A and Figure 2}) \). After correction for multiple comparisons, the medial and inferior temporal lobes and a small area in the midbrain remained involved \( (P < .01) \).

**aMCI-MD Group**

The aMCI-MD group also showed a pattern of gray matter loss predominantly affecting the medial and inferior temporal lobes, compared with the control group \( (P < .001, \text{uncorrected for multiple comparisons; Figure 1B}) \). However, loss extended back into the midbrain, posterolateral and basal temporal lobes, the posterior cingulate, and the parietal association cortex and forward into the anterior insula and medial frontal lobe \( (P < .001, \text{uncorrected for multiple comparisons}) \). Loss was bilateral but slightly greater on the left. Loss in all of these regions remained after correction for multiple comparisons \( (P < .01) \).

**naMCI-SD Group**

The naMCI-SD group showed a widespread pattern of gray matter loss involving the temporal lobes, including the amygdala, hippocampus and entorhinal cortex, basal forebrain, left hypothalamus, lateral superior frontal lobes, parietal lobes, and occipital lobes compared with the control group \( (P < .001, \text{uncorrected for multiple comparisons; Figure 1C}) \). No regions remained after correction for multiple comparisons \( (P < .01) \).

**naMCI-MD Group**

The only regions of gray matter loss to reach significance in the naMCI-MD group compared with the control group were found in the lateral anterior parietal lobes \( (P < .001, \text{uncorrected for multiple comparisons; Figure 1D}) \). No regions remained after correction for multiple comparisons \( (P < .01) \).

**Individual naMCI Domains**

The subgroup of subjects with naMCI-SD with language impairment showed a pattern of gray matter loss affecting the left anterior inferior and medial temporal lobes, compared with the control group \( (P < .001, \text{uncorrected for multiple comparisons; Figure 3}) \). There was also some minor involvement of the right temporal lobes.
lobe and the left parietal lobe. The naMCI-SD subgroup with attention/executive impairment showed gray matter loss in the basal forebrain, particularly the nucleus basalis of Meynert and the diagonal band of Broca (Figure 4A and B), and the medial septum of the hypothalamus, compared with the control group ($P < .001$, uncorrected for multiple comparisons; Figure 4A). Some other scattered regions of loss were identified, although the significance of loss in these regions is uncertain. The subgroup of subjects with naMCI-SD with impaired visuospatial skills showed a scattered pattern of gray matter loss predominantly affecting the frontolateral lobes and the floor of the occipital horn of the lateral ventricle bilaterally, compared with the control group ($P < .001$, uncorrected for multiple comparisons; Figure 5). Loss was also found in the posterior right hippocampus and the lateral posterior temporal lobe. No regions in any of these comparisons remained after correction for multiple comparisons ($P < .01$).

**COMMENT**

In this study, we categorized patients with MCI into subgroups on the basis of deficit patterns present in specific cognitive domains. This method of MCI subclassification has been previously described and is currently used in both the Alzheimer Disease Neuroimaging Initiative study and the National Institute on Aging Alzheimer’s Disease Centers Program for the Uniform Data Set. All previous Mayo Clinic imaging studies of MCI analyzed only subjects with aMCI-SD and aMCI-MD. The current study shows that the various MCI groups demonstrate different patterns of atrophy on MRI, and these patterns may provide clues as to the future course and etiology of MCI subtypes.

Gray matter loss in both the aMCI-SD and aMCI-MD groups focused on the medial temporal lobes. The aMCI-MD group also showed loss spreading into the posterior lateral and basal temporal lobes, the posterior cin-
the anterior insula, and the medial frontal lobe. These regions of atrophy are typical of AD and fit nicely with the proposed scheme of pathologic progression of disease in AD in which neurofibrillary tangle deposition starts in the entorhinal cortex and hippocampus before spreading into the isocortical association areas. These imaging results, therefore, suggest that both aMCI-SD and aMCI-MD are likely to progress to AD. Follow-up data show that in a high percentage of these subjects, MCI ultimately progressed to AD. The atrophy was more widespread in the aMCI-MD group, most likely reflecting the more widespread cognitive impairment and perhaps suggesting that in these subjects the disease will progress to AD sooner than in the aMCI-SD group. This suggestion is supported by the lower DRS score observed in the aMCI-MD group and by a recent study that showed increased mortality in subjects with aMCI-MD compared with aMCI-SD. The frequency of APOE ε4 carriers was also high in both the aMCI-SD and aMCI-MD groups, providing further evidence that, in these subjects, MCI is highly likely to progress to AD. The APOE ε4 allele is associated with an increased risk of AD and can aid in the prediction of progression to MCI and dementia. A minority of subjects in the aMCI-MD group, however, progressed to non-AD dementias. This is not unexpected given the heterogeneity in cognitive deficits and because the amnestic deficit was not necessarily the most prominent feature. Note that, although aMCI is likely to progress to AD, all subjects in this study had normal activities of daily living skills and, thus, by definition, could not be classified as having AD. This is a particularly important distinction in subjects with aMCI-MD who had impairments in both memory and 1 or more non-memory domains.

Previous studies of aMCI and preclinical AD have similarly shown that the focus of loss is in the medial temporal lobes, particularly involving the hippocampus. Isocortical association areas, including the parietal, temporal, and frontal lobes and the posterior cingulate, have also been implicated, although to a lesser degree. To our knowledge, only 1 other study has been published that explicitly classified MCI into single- and multiple-domain subtypes. These authors also showed relatively restricted loss in the medial temporal lobe in the aMCI-SD group and a more diffuse and extensive pattern of loss in the aMCI-MD group. However, the number of subjects in the single-domain group was small (n = 9), and the multiple-domain group seems to have been composed of a mix of subjects with aMCI and naMCI.

In contrast to the well-defined patterns of gray matter loss in subjects with aMCI in our study, those with naMCI-SD and naMCI-MD showed scattered patterns of loss without any particular focus. The hippocampus and medial temporal lobes were not the main focus of loss, consistent with the lack of significant memory impairment in these subjects. The follow-up data also showed that these subjects were less likely to progress to AD than subjects with aMCI-SD. The naMCI groups are, however, highly heterogeneous, with subjects showing impairment in various cognitive domains. The subjects in the naMCI-SD group were therefore subdivided into those with a language, attention/executive, or visuospatial deficit. Subjects with naMCI-SD with language impairment showed a pattern of loss predominantly affecting the left anterior inferior and medial temporal lobes; that is, the imaging pattern was highly consistent with the observed clinical deficit. This pattern is similar to that reported in subjects with a language variant of frontotemporal dementia. However, the APOE ε4 frequency in this group (50%) was higher and the age was older than one might expect in frontotemporal dementia. The high frequency of APOE ε4 in this subgroup may instead be indicative of AD. Subjects with language impairments can have AD at pathologic analysis and a left-sided pattern of atrophy. Disease in most of these subjects did progress to a clinical diagnosis of AD, although in a few subjects it progressed to a non-AD dementia, including frontotemporal dementia. The naMCI-SD group with attention/executive impairment showed gray matter loss in the basal nucleus of Meynert, the diagonal band of Broca, and the hypothalamus. These regions are key nuclei of the cholinergic system, which is an essential component of neuronal systems mediating attentional function. Deficits in the cholinergic system have been associated with AD but also with dementia with Lewy bodies. Cholinergic dysfunction occurs earlier in the disease course in dementia with Lewy bodies than in AD. A recent MRI study has also shown that these regions are involved in dementia with Lewy bodies. These subjects had a relatively low APOE ε4 frequency (33%), suggesting that some of them may not demonstrate the pathologic features of AD. Follow-up data showed that, although 3 cases progressed to a clinical diagnosis of AD, disease in 2 subjects progressed to dementia with Lewy bodies. Subjects in the naMCI-SD group who had a visuospatial deficit showed no coherent pattern of atrophy, although they showed low APOE ε4 frequency.
published with similar numbers per subject group, both with and without correction for multiple comparisons. The power of VBM to detect significant differences depends critically on the interaction between biological effect size and sample size. The more robust pattern of loss observed in the aMCI groups could be the result of the large number of subjects in these groups, as well as the strong medial temporal lobe biological signal and its coherence across subjects within the aMCI groups. The preponderance of aMCI in our cohort likely reflects the recruitment mechanism at our center, which until recently has emphasized memory impairment. The prevalence percentages of the MCI subtypes in a population are unknown, although this is an area of active research.44 Follow-up data were available for these subjects with MCI, but they should be considered preliminary because the follow-up was too short to allow thorough characterization. In addition, pathologic confirmation was not available. There are also several limitations inherent in the technique of VBM. In particular, misclassification of tissue as a result of variable degrees of ventricular enlargement among subjects is likely to have contributed to the artifactual gray matter loss observed around the lateral ventricles in the amnestic groups (Figure 1A and B). Voxel-based morphometry also may not be equally sensitive to volume loss in all areas of the brain. The power to detect a difference is limited in regions that show greater normative variability. It is important to stress that VBM examines group data and, therefore, the results should be interpreted at the group/concept level rather than the single-subject level.

The patterns of gray matter loss observed in this study are consistent with the well-established facts that aMCI, for the most part, progresses to AD and the anatomical signature of prodromal AD is medial temporal atrophy. The more widespread pattern of loss in the subjects with aMCI-MD suggests that the disease has progressed farther in the clinical course to AD than in the subjects with aMCI-SD. Given that AD has a prodromal syndrome, that is, aMCI, it is almost certain that other neurodegenerative dementias do also and that each should have its own imaging signature. Although the results in the nMCI groups did not survive correction for multiple comparisons, they suggest that in some of these subjects, MCI may progress to neurodegenerative dementias other than AD. Longitudinal follow-up studies are currently under way to validate this hypothesis.

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