Depressive Symptoms in Mild Cognitive Impairment Predict Greater Atrophy in Alzheimer's Disease-Related Regions

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Background: Depression has been associated with higher conversion rates from mild cognitive impairment (MCI) to Alzheimer's disease (AD) and may be a marker of prodromal AD that can be used to identify individuals with MCI who are most likely to progress to AD. Thus, we examined the neuroanatomical changes associated with depressive symptoms in MCI.

Methods: Two-hundred forty-three MCI subjects from the Alzheimer's Disease Neuroimaging Initiative who had brain magnetic resonance imaging scans at baseline and 2-year follow-up were classified into depressed ($n = 44$), nondepressed with other neuropsychiatric symptoms ($n = 93$), and no-symptom (NOSYMP; $n = 106$) groups based on the Neuropsychiatric Inventory Questionnaire. Tensor-based morphometry was used to create individual three-dimensional maps of 2-year brain changes that were compared between groups.

Results: Depressed subjects had more frontal ($p = .024$), parietal ($p = .030$), and temporal ($p = .038$) white matter atrophy than NOSYMP subjects. Those whose depressive symptoms persisted over 2 years also had higher conversion to AD and more decline on measures of global cognition, language, and executive functioning compared with stable NOSYMP subjects. Nondepressed with other neuropsychiatric symptoms and NOSYMP groups exhibited no differences in rates of atrophy.

Conclusions: Depressive symptoms were associated with greater atrophy in AD-affected regions, increased cognitive decline, and higher rates of conversion to AD. Depression in individuals with MCI may be associated with underlying neuropathological changes, including prodromal AD, and may be a potentially useful clinical marker in identifying MCI patients who are most likely to progress to AD.

Mild cognitive impairment (MCI) [1] is conceptualized as a transitional state between normal aging and early Alzheimer's disease (AD). In longitudinal studies, individuals meeting criteria for MCI are at increased risk for progressing to AD compared with age-matched control subjects [1,2]. However, rates of conversion from MCI to AD are highly variable [3] because the cognitive deficits exhibited by these individuals may be related to a number of different pathologies. In an effort to detect AD in prodromal stages, there have been attempts to identify subgroups of MCI patients who are at highest risk for progression to AD. Many approaches focus on identifying early biological markers in structural [4] and functional [5] neuroimaging and cerebrospinal fluid [6], but clinical tools, such as neuropsychological testing [7], have also been useful.

Another potential clinical marker for identifying MCI individuals at high risk of developing AD is the presence of neuropsychiatric symptoms. Depression, in particular, has been associated with increased risk of dementia [8,9]. We previously demonstrated that depressive symptoms predicted progression to AD in MCI patients [10,11], but the neurobiological mechanism underlying this association is not yet fully understood. In several cross-sectional studies, depressed elderly appear to have underlying brain changes associated with AD, including reduced temporal lobe [12], hippocampal, and amygdala volume [13,14]. As depressive symptoms may be a clinical marker of prodromal AD, we wanted to extend the findings in the existing literature and demonstrate that depressive symptoms would be associated with AD-related neuroanatomical changes, particularly in white matter regions.

Tensor-based morphometry (TBM) is a relatively novel computational approach that can compare longitudinally acquired images and visualize the spatial profile of brain atrophy over time, including estimates of tissue volume loss at each voxel in the brain [15]. This approach has been successfully used to track longitudinal changes associated with normal brain aging and neurodegenerative disorders [16,17]. Also, it may be more sensitive in detecting changes in white matter volume, as it does not require a segmentation step, thus avoiding potential errors in accurate tissue classification. We applied TBM to compare patterns of brain atrophy in MCI patients with and without depressive symptoms. Specifically, we hypothesized that MCI patients with depressive symptoms would demonstrate greater brain atrophy over 2 years compared with those without depressive symptoms in regions specifically associated with AD pathology.

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Methods and Materials

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography, and other biological markers can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, M.D., Veterans Affairs Medical Center and University of California-San Francisco. The Alzheimer's Disease Neuroimaging Initiative is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research—approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information, see www.adni-info.org.

Participants

Baseline and 2-year follow-up MRI scans were downloaded from the ADNI public database (http://www.loni.ucla.edu/ADNI/Data/) on or before June 1, 2010, and reflect the status of the database at that point. Subjects were excluded if they had significant neurologic disease other than AD, abnormal baseline MRI scan or contraindications to MRI, psychiatric disorder, substance abuse or dependence within the last 2 years, and medical illnesses that could affect cognition or protocol compliance. Please refer to the ADNI protocol for detailed inclusion and exclusion criteria (18).

We analyzed baseline and 2-year follow-up MRI scans from 243 individuals (162 male subjects; mean age at baseline: 75.1 ± 6.9 years; age 55–90) who were diagnosed with amnestic MCI at baseline. The average length of time between baseline and follow-up scans was 2.09 years (SD = .09; range = 1.82–2.73 years). Diagnosis of MCI was made according to the criteria by Petersen *et al.* (1), in that all MCI subjects demonstrated objective memory impairment but did not meet criteria for dementia. Specifically, they had a Mini-Mental State Examination (MMSE) (19) score of 24 or higher, a global Clinical Dementia Rating (20) score of .5, a Clinical Dementia Rating memory score of .5 or higher, and an impaired score on delayed recall of Story A on the Wechsler Memory Scale-Revised (21).

The study was conducted according to the Good Clinical Practice guidelines, the Declaration of Helsinki, and U.S. 21 Code of Federal Regulations Part 50 –Protection of Human Subjects and Part 56 –Institutional Review Boards. Written informed consent was obtained from all participants before experimental procedures were performed.

Neuropsychological Assessment

All subjects underwent thorough clinical and neuropsychological assessment at the time of scan acquisition. Neurocognitive tests included the following domains and measures: global cognitive functioning was assessed using the MMSE (19). The delayed recall trial of the Rey Auditory Verbal Learning Test (22) provided a measure of auditory verbal memory. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span subtest (23) was used to measure attention. Language abilities were assessed using the Boston Naming Test (24), which is a measure of object naming, and Animals and Vegetables (25), which are measures of semantic verbal fluency. The WAIS-R Digit Symbol subtest (23) and Trail Making Test (Trails A and Trails B) (26) are measures of psychomotor speed and visuospatial tracking. Trails B additionally assesses executive abilities, including cognitive flexibility and divided attention. Complete details of the ADNI assessments are found in the *ADNI Procedures Manual* (http://www.adni-info.org/Scientists/Pdfs/adniproceduresmanual12.pdf).

Neuropsychiatric Assessment

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q) (27), a caregiver-based instrument that measures the presence (1 = yes, 0 = no) and severity (1 = mild, 2 = moderate, 3 = severe) over the prior month of 12 symptom domains: delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior, nighttime disturbances, and eating disturbances. Study participants were divided into three groups based on baseline NPI-Q scores: individuals with depressive symptoms (DEP), defined as having a score of 1 on the depression domain, regardless of the presence or absence of other neuropsychiatric symptoms; individuals with a score of 0 on the depression domain but a score of 1 on any of the other 11 domains (OTHER); and individuals with no psychiatric symptoms or scores of 0 across all 12 domains (NOSYMP). Subjects meeting criteria for major depression were excluded from ADNI; thus, any reported depressive symptoms are subsyndromal and unrelated to a premorbid psychiatric disorder.

MRI Acquisition and Image Correction

All subjects were scanned with a standardized MRI protocol developed for ADNI (28). Briefly, high-resolution structural brain MRI scans were acquired at 59 sites using 1.5T MRI scanners. Although different scanner types (General Electric Healthcare, Pewaukee, Wisconsin; Philips Medical Systems, Andover, Massachusetts; Siemens Medical Solutions, Malvern, Pennsylvania) and various software platforms were used, a standardized MRI protocol was used to maximize cross-site comparability (28). A sagittal three-dimensional magnetization prepared rapid acquisition gradient-echo scanning protocol was used with the following acquisition parameters: repetition time of 2400 milliseconds, minimum full echo time, inversion time of 1000 milliseconds, 8° flip angle, 24 cm field of view, and $192 \times 192 \times 166$ acquisition matrix in the x, y, and z dimensions, yielding a voxel size of $1.25 \times 1.25 \times 1.2$ mm^3, later reconstructed to 1 mm isotropic voxels.

Image corrections were applied using a processing pipeline at the Mayo Clinic, consisting of 1) correction of geometric distortion due to gradient nonlinearity (29), i.e., "gradwarp"; 2) B1-correction for adjustment of image intensity inhomogeneity due to B1-non-uniformity (28); 3) N3 bias field correction for reducing residual intensity inhomogeneity (30); and 4) geometrical scaling for removing scanner and potential session-specific calibration errors using a phantom scan acquired for each subject (31). All original image files, as well as images with all of these corrections, are available to the general scientific community at http://www.loni.ucla.edu/ADNI/Data/.

Image Preprocessing

First, each subject's follow-up scan was linearly registered to their baseline scan, with a 9-parameter transformation driven by a mutual information cost function (32), to adjust for global differ-

ences in position and scale across time. Second, to account for global brain shape and size differences across subjects, the mutually aligned scan pairs were then linearly registered to the International Consortium for Brain Mapping template (ICBM-53) (33), applying the same 9-parameter transformation to both scans. Globally aligned images were resampled in an isotropic space of 220 voxels along x, y, and z dimensions with a final voxel size of 1 mm^3.

Tensor-Based Morphometry and Three-Dimensional Maps of Atrophic Rates

Jacobian maps were created for each individual by nonlinearly warping follow-up scans to match baseline scans of the same individual using a nonlinear, inverse-consistent elastic intensity-based registration algorithm driven by a mutual information cost function (34). A color-coded map of the Jacobian determinants was computed from the gradient of the deformation field to illustrate regions of volume expansion (15) over the 2-year interval, yielding a map that estimates the amount of tissue volume change at each voxel. Jacobian maps were also spatially normalized across subjects by nonlinearly aligning all individual maps to a minimal deformation template (MDT) for regional comparisons and group statistical analysis. The MDT represents the average shape of 40 healthy elderly control subjects; the procedure to construct the MDT is detailed in Hua *et al.* (35). Average maps were computed by taking the mean at each voxel of the Jacobian maps across subjects.

Regions of Interest

The regions of interest, comprised of frontal, temporal, parietal, and occipital lobes, were manually hand-traced by a trained anatomist on the MDT to generate binary masks for each lobe, which were subsequently used to summarize brain atrophy at a regional level in each group. Within each lobe, tissue types were distinguished by creating maps of gray and white matter, cerebrospinal fluid (CSF), and nonbrain tissues using the partial volume classification algorithm from the BrainSuite software package (Laboratory of Neuroimaging at the University of California Los Angeles) (36).

Statistical Analyses

To illustrate systematic differences in atrophic rates between the DEP, OTHER, and NOSYMP groups, we constructed voxelwise statistical maps based on the Student *t* statistic. The Jacobian maps were compared between groups using permutation-based two-sample *t* tests to assess overall significance of group differences inside each region of interest, corrected for multiple comparisons (37). In brief, a null distribution for the group differences in tissue volume change (Jacobian values) at each voxel was constructed using 10,000 random permutations of the data. For each test, the subjects' group status (e.g., DEP vs. NOSYMP) was randomly permuted and voxelwise *t* tests were conducted to identify voxels more significant than $p = .05$. The volume of voxels inside a mask (i.e., temporal lobes) more significant than $p = .05$ was computed for the real experiment and for the random assignments. A ratio, describing the fraction of the time suprathreshold volume was more extreme in the randomized tests than the original test, was calculated to yield an overall *p* value for the significance of the map (corrected for multiple comparisons by permutation).

For group comparisons of neuropsychological performance, a one-way analysis of variance was performed, followed by Scheffe tests for post hoc analysis of significant group differences. Group differences in rates of conversion from MCI to dementia were compared using chi-square analyses.

Results

Demographic Characteristics

Of 243 MCI subjects, 44 were in the DEP group, 93 were in the OTHER group, and 106 were in the NOSYMP group. The three groups did not differ on any demographic characteristics (Table 1). The mean severity of depressive symptoms in the DEP group was 1.30 (SD = .51). Thirty-two (73%) were rated as mild in severity, 11 (25%) were rated as moderate, and 1 (2%) was rated as severe. Thirty-five of the 44 subjects in the DEP group also endorsed at least one other symptom on the NPI-Q. The most commonly endorsed comorbid symptoms were irritability (45.5%) and anxiety (31.8%).

Table 1. Demographic Characteristics of MCI Groups

Demographic Variables	Group Status at Baseline				
	DEP (*n* = 44) Mean (SD)	OTHER (*n* = 93) Mean (SD)	NOSYMP (*n* = 106) Mean (SD)	$F(2,240)$ or χ^2	*p*
Age at baseline, years	75.0 (6.8)	74.8 (7.0)	75.3 (6.9)	.27	.77
Education, years	16.4 (2.9)	15.8 (2.9)	15.7 (3.1)	1.22	.30
Gender (M/F)	29M/15F	63M/30F	70M/36F	.63	.96
Race, % Caucasian	96%	95%	93%	.39	.82

Demographic Variables	Group Status Stable at 2-Year Follow-up			
	DEP-Stable (*n* = 21) Mean (SD)	NOSYMP-Stable (*n* = 51) Mean (SD)	$F(1,70)$ or χ^2	*p*
Age at baseline, years	74.8 (7.5)	75.7 (7.3)	.19	.66
Education, years	16.9 (2.8)	16.3 (2.7)	.77	.38
Gender (M/F)	12M/9F	35M/16F	.87	.35
Race, % Caucasian	100%	92%	1.74	.42

Demographic characteristics are presented for the DEP, OTHER, and NOSYMP groups, as well as the DEP-stable and NOSYMP-stable subgroups. Group differences in age and education were assessed using analysis of variance. Group differences in gender distribution and race composition were assessed using Pearson chi-square tests.

DEP, subjects with depressive symptoms; DEP-Stable, subjects with depressive symptoms who remained depressed at 2-year follow-up; F, female; M, male; MCI, mild cognitive impairment; NOSYMP, subjects with no psychiatric symptoms; NOSYMP-Stable, subjects with no psychiatric symptoms who continued to exhibit no psychiatric symptoms at 2-year follow-up; OTHER, nondepressed subjects with other neuropsychiatric symptoms.

Prevalence rates and mean severity scores for each NPI-Q domain are reported in Table S1 in Supplement 1. Twenty-one subjects (48%) in the DEP group were on antidepressant medications, 22 (50%) were not on antidepressants, and 1 subject (2%) had no information regarding antidepressant use. Antidepressant use was not associated with differences in depression severity at baseline [$F(1,41) = .27, p = .61$] or change in depression severity at 2-year follow-up [$F(1,18) = 1.96, p = .18$].

At 2-year follow-up, 21 of the 44 DEP subjects remained depressed (DEP-stable), whereas 20 no longer reported depressive symptoms. Data for the NPI-Q at 2-year follow-up was unavailable for the remaining three subjects. Of the 106 NOSYMP subjects, 51 continued to exhibit no psychiatric symptoms (NOSYMP-stable), 51 developed psychiatric symptoms, and 4 had no NPI-Q data at 2-year follow-up. Secondary analyses were performed on the subset of participants who had stable psychiatric symptoms and group status (i.e., DEP-stable or NOSYMP-stable) at 2-year follow-up. Demographic characteristics are reported in Table 1. The mean severity of depressive symptoms in the DEP-stable group was 1.38 (SD = .59) at baseline and 1.29 (SD = .46) at 2-year follow-up. At baseline, 14 DEP-stable subjects were rated as mild in severity, 6 were rated as moderate, and 1 was rated as severe. At follow-up, 15 were rated as mild in severity, and 6 were rated as moderate.

TBM: Brain Atrophy Rates

Individual Jacobian maps were averaged within each DEP, OTHER, and NOSYMP group to demonstrate the mean volume loss (in blue) and ventricular enlargement (in red) in each group (Figure 1), thus providing a voxelwise estimate of the amount of atrophy over 2 years. The resulting statistical maps from direct group comparisons (Figure 2) revealed significantly more atrophy over 2 years in the frontal, parietal, and temporal white matter regions of the DEP group relative to the NOSYMP group. Permutation tests (corrected for multiple comparisons) revealed that the DEP group had significantly more atrophy than the NOSYMP group over 2 years in the frontal ($p = .024$) and parietal ($p = .030$) white matter, left greater than right, and in the bilateral temporal white matter ($p = .038$). In contrast, statistical comparisons between the OTHER and NOSYMP groups revealed no significant regional differences in atrophy. Direct comparison of the DEP group with the OTHER group revealed greater atrophy of the frontal white matter, which was statistically significant on the left ($p = .045$) but not on the right ($p = .107$) after correcting for multiple comparisons.

Average Jacobian maps of the DEP-stable and NOSYMP-stable groups are shown in Figure 3. Voxelwise statistical comparison (Figure 2D) and permutation tests revealed greater overall white matter atrophy ($p = .044$) in the DEP-stable group compared with the NOSYMP-stable group. Specifically, the DEP-stable group exhibited more frontal ($p = .027$), parietal ($p = .048$), and temporal ($p = .026$) white matter atrophy bilaterally than the NOSYMP-stable group.

Rates of Conversion from MCI to AD

Rates of conversion from MCI to AD are shown in Table 2. The DEP group had a 50% rate of conversion from MCI to AD within 2 years, which was higher than the OTHER (40%) and NOSYMP (34%) groups, though the difference was nonsignificant ($\chi^2 = 3.39, p = .184$). The DEP-stable group, however, demonstrated a significantly higher rate of conversion to AD (62%) compared with the NOSYMP-stable group (27%; $\chi^2 = 7.53, p = .006$).

Performance on Cognitive Measures

At baseline, there were no significant differences ($p > .05$) in neuropsychological test performance among the three groups in
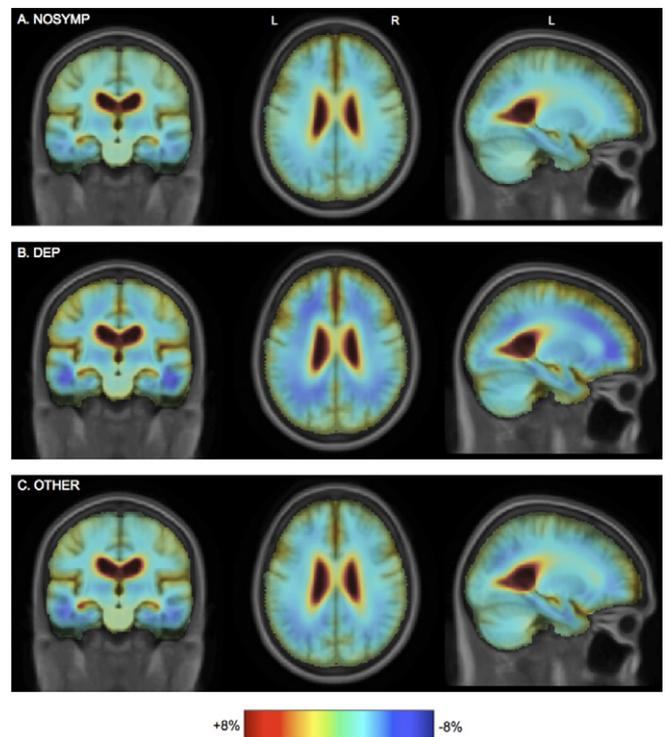

Figure 1. Jacobian maps showing the mean 2-year atrophy of brain tissue (in blue color) and ventricular enlargement (in red color) for the subjects with no psychiatric symptoms (NOSYMP) **(A)**, depressive symptoms (DEP) **(B)**, and nondepressed with other neuropsychiatric symptoms (OTHER) **(C)**. These tissue changes are shown as percentages, relative to the baseline scan, and are computed within each individual before averaging across subjects in the group. L, left; R, right.

any of the cognitive domains. At 2-year follow-up, there were no significant group differences in the relative change in test scores from baseline to follow-up, except for a measure of working memory [WAIS-R Digit Span-backward; $F(2,234) = 3.76, p = .03$]. Specifically, Scheffe post hoc tests revealed that the OTHER group (M = $-.74$, SD = 1.74) had greater decline on Digit Span-backward compared with the NOSYMP group (M = $-.01$, SD = 1.94; $p = .02$). The DEP group did not differ significantly from either the NOSYMP group or OTHER group on this task. Baseline scores and relative change in scores at follow-up for each test are provided in Table S2 in Supplement 1.

The DEP-stable and NOSYMP-stable groups also performed similarly ($p > .14$) on all neuropsychological tests at baseline. At 2-year follow-up, the DEP-stable group demonstrated significantly more decline from baseline scores than the NOSYMP-stable group on the MMSE [$F(1,70) = 7.45, p = .01$; DEP-stable: M = -2.19, SD = 3.75; NOSYMP-stable: M = $-.12$, SD = 2.53], Boston Naming Test [$F(1,70) = 14.44, p < .01$; DEP-stable: M = -1.48, SD = 2.91; NOSYMP-stable: M = .84, SD = 2.09], Vegetables [$F(1,70) = 5.55, p = .02$; DEP-stable: M = -2.24, SD = 2.47; NOSYMP-stable: M = $-.20$, SD = 3.63], and Trails B [$F(1,70) = 6.40, p = .01$; DEP-stable: M = 38.79 sec, SD = 63.87; NOSYMP-stable: M = .92 sec, SD = 52.45]. Baseline scores and relative change in scores at follow-up of the DEP-stable and NOSYMP-stable groups are provided in Table S3 in Supplement 1.

Discussion

Using TBM, we demonstrated that MCI subjects with depressive symptoms exhibited significantly more atrophy over 2 years com-
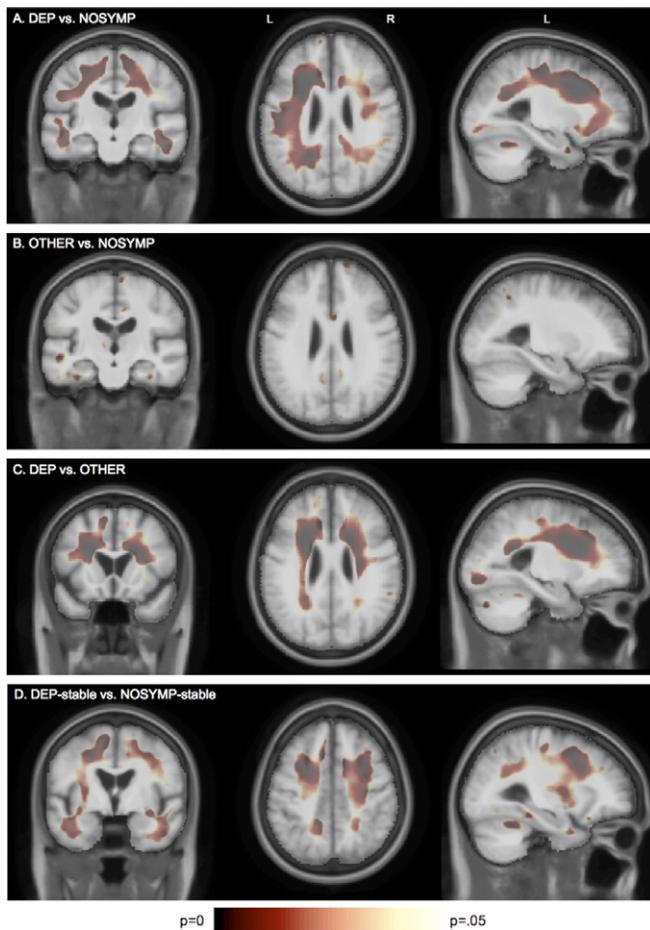
Figure 2. Statistical *p* maps showing significant differences in brain atrophy over 2 years between the subjects with depressive symptoms (DEP), with no psychiatric symptoms (NOSYMP), and nondepressed with other neuropsychiatric symptoms (OTHER) and between the DEP subjects who remained depressed at 2-year follow-up (DEP-stable) and NOSYMP subjects who continued to exhibit no psychiatric symptoms at 2-year follow-up (NOSYMP-stable). The DEP group demonstrated significantly greater atrophy over 2 years (as indicated in brown color) than the NOSYMP group in the left frontal and parietal lobes and bilateral temporal lobes, particularly involving the white matter **(A)**. No significant difference in atrophy was observed between OTHER and NOSYMP groups **(B)**. The DEP group exhibited greater frontal white matter atrophy than the OTHER group **(C)**. The DEP-stable group demonstrated significantly greater atrophy than the NOSYMP-stable group in the bilateral frontal, parietal, and temporal white matter regions **(D)**. L, left; R, right.

pared with those without any neuropsychiatric symptoms. This finding, coupled with the lack of detectable differences between the OTHER and NOSYMP groups, highlights the specificity of the relationship between depressive symptoms and the observed brain changes. Moreover, the DEP group demonstrated greater atrophy, even when compared directly with the OTHER group. Subjects in the DEP group with persistent symptoms over 2 years also demonstrated more decline on select neuropsychological tests and had higher rates of conversion to AD compared with the stable NOSYMP subjects. Depression has previously been demonstrated to be a potentially useful clinical marker for identifying MCI subjects who are more likely to progress to AD (10,11). To our knowledge, this is the first study to map the neurobiological effects underlying the predictive function of depressive symptoms associated with increased progression to AD.

Prior literature on the neuroanatomical correlates of depression in healthy elderly subjects has found reduced volume in the frontal lobes and anterior cingulate (38), as well as hippocampus and amygdala (13,14). Our findings were consistent with these past reports; however, we also observed significant white matter atrophy in parietal and temporal lobes, regions known to be affected in AD. Greater atrophy was observed on the left than the right. This asymmetry has also been observed in previous studies that found greater atrophy and metabolic dysfunction in the left hemisphere of AD patients (39,40), suggesting greater vulnerability of the left hemisphere to neurodegeneration in AD. A similar pattern has also been shown in MCI subjects who had higher levels of Pittsburgh Compound-B retention on the left dorsal frontal cortex and sensorimotor cortex compared with the right (41). Hence, the pattern of atrophy in the DEP group may reflect shared underlying changes in the neuroanatomical correlates of both depressive symptoms and pathological changes associated with AD (42). This is consistent with our previous findings demonstrating that depressive symptoms represent a phenotypic marker related to the onset of AD and favorable response to donepezil therapy (10), along with other studies that have found increased AD-related pathology in depressed elderly with cognitive impairment, including elevated retention of positron emission tomography radioligands for beta-amyloid 1-42 ($A\beta42$) and tau (43,44) and higher burden of $A\beta42$-containing neuritic plaques and tau-containing neurofibrillary tangles at autopsy (45). Qiu *et al.* (46) found that depressed elderly subjects demonstrated lower plasma-$A\beta42$ levels compared with nondepressed elderly. In our sample, post hoc analysis of CSF biomarker concentrations available for a subgroup of participants (*n* = 129) revealed no significant differences between the DEP, OTHER, and NOSYMP groups in mean concentrations of $A\beta42$, tau, or phosphorylated-tau or in the prevalence of subjects meeting AD-signature cutoff values (6) in any of these CSF biomarkers (Tables S4 and S5 in Supplement 1). However, the cohort studied by Qiu *et al.* (46) had clinically significant levels of depression, whereas our DEP group was subclinical and, on average, mild in severity. Thus, differ-
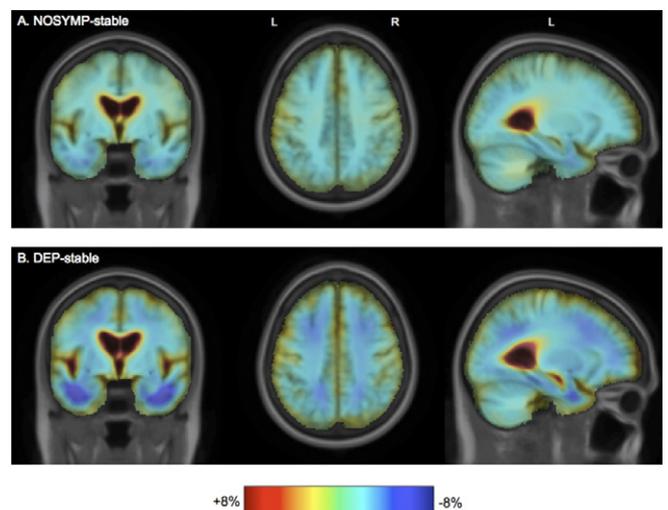

Figure 3. Average Jacobian maps demonstrating change in brain volume over 2 years in the subjects with no psychiatric symptoms who continued to exhibit no psychiatric symptoms at 2-year follow-up (NOSYMP-stable, **A**) and subjects with depressive symptoms who remained depressed at 2-year follow-up (DEP-stable, **B**). These tissue changes are shown as percentages, relative to the baseline scan, and are computed within each individual before averaging across subjects in the group. L, left; R, right.

Table 2. Rates of Conversion from MCI to AD Within 2 Years

	Group Status at Baseline				
Conversion Status	DEP (*n* = 44) *n* (%)	OTHER (*n* = 93) *n* (%)	NOSYMP (*n* = 106) *n* (%)	χ^2	*p*
No conversion	22 (50%)	56 (60%)	70 (66%)	3.39	.184
Conversion	22 (50%)	37 (40%)	36 (34%)		
	Group Status Stable at 2-Year Follow-up				
Conversion Status	DEP-Stable (*n* = 21) *n* (%)	NOSYMP-Stable (*n* = 51) *n* (%)		χ^2	*p*
No conversion	8 (38%)	37 (73%)		7.53	.006
Conversion	13 (62%)	14 (27%)			

The number of subjects who maintained a diagnosis of MCI from baseline to 2-year follow-up (No conversion) and those who converted from MCI to AD by the 2-year follow-up visit (Conversion) are reported. Group differences in the prevalence (%) of subjects who converted to AD were assessed using Pearson chi-square tests.

AD, Alzheimer's disease; DEP, subjects with depressive symptoms; DEP-Stable, subjects with depressive symptoms who remained depressed at 2-year follow-up; MCI, mild cognitive impairment; NOSYMP, subjects with no psychiatric symptoms; NOSYMP-Stable, subjects with no psychiatric symptoms who continued to exhibit no psychiatric symptoms at 2-year follow-up; OTHER, nondepressed subjects with other neuropsychiatric symptoms.

ences in CSF biomarker concentrations associated with depression may be underestimated in our sample.

Despite the increased evidence of a possible shared pathophysiology between depression and AD, the mechanism underlying this relationship is not fully elucidated but seems to involve white matter. In our study, the brain changes associated with depressive symptoms were largely confined to white matter. Some investigators have found reduced white matter volume in depressed individuals (47), and recent investigations using diffusion tensor imaging have identified lower fractional anisotropy in prefrontal regions, anterior cingulate, and temporal regions in depressed subjects (48). Severe depression and other neuropsychiatric disorders have also been associated with abnormal myelination (49,50) and reduced or abnormal oligodendrocytes (51), especially at older ages (52).

Beyond the association between white matter and depression, the white matter atrophy may be a direct consequence of AD pathology. Substantial theoretical and empirical evidence supports white matter pathology in AD (42,53). Myelin breakdown has also been observed at the MCI stage (54,55). Furthermore, depressive symptoms that were persistent over 2 years were associated not only with white matter atrophy but also more cognitive decline on measures of global cognition, language, and executive abilities, as well as higher rates of conversion to AD compared with MCI subjects with no psychiatric symptoms. Thus, the white matter changes elucidated by the presence of depressive symptoms may be interpreted as a shared early pathological process of AD rather than representative of neuroanatomical changes associated with depression alone. Post hoc analyses revealed that within the NOSYMP group, subsequent development of psychiatric symptoms at 2-year follow-up was associated with greater right frontal white matter atrophy (*p* = .033), a trend toward greater right temporal white matter atrophy (*p* = .053), and higher rate of conversion to AD (47% vs. 27%; χ^2 = 4.19, *p* = .041). This finding lends further support to the hypothesis that the development of new psychiatric symptoms in MCI may be a symptom reflecting the underlying progression of AD pathology.

The strengths of this study include the prospective design in which each subject acts as his/her own control and measurement of intraindividual rates of change yield greater sensitivity to detect subtle brain changes over time. Several limitations should also be acknowledged. First, the acquisition of MRI scans from multiple centers raises the possibility of interscanner and software variability. However, a standardized MRI protocol was used across all 59 sites to maximize cross-site comparability (28). Second, although the current study focused on depressive symptoms, there was significant comorbidity in the DEP group, with almost 80% of subjects endorsing at least one other symptom on the NPI-Q. Further, the ADNI protocol specifically excluded patients with clinically significant depressive symptoms constituting a diagnosis of major depression. However, the prevalence rates of depressive and other neuropsychiatric symptoms in our sample are comparable with those reported in other large MCI cohorts, including the National Alzheimer's Coordinating Center database (56) and the population-based Cardiovascular Health Study (57). Moreover, as these symptoms are now recognized to be prevalent in MCI patients and may have predictive value in identifying individuals at higher risk of progressing to AD, the differences we found may even be underestimated. Third, even though the NPI-Q has been demonstrated to provide adequate test-retest reliability and convergent validity for assessing a broad range of neuropsychiatric symptoms (27), it is not designed as a detailed or comprehensive measure of depressive symptoms; therefore, the inclusion of a more precise instrument is necessary for future studies of the depression risk for developing dementia. Fourth, the present study sample was predominantly Caucasian, male, and highly educated, which may limit the generalizability of the results to more demographically diverse community-based samples. Finally, future studies should examine subregions of the broad lobar atrophy reported here to further explore the neurobiological substrates of the complex relationship between depression and dementia in the elderly.

Analysis of serial MRI scans using TBM appears to be sensitive in tracking distinct patterns of brain changes within a population of MCI patients. Specifically, the presence of depressive symptoms was associated with greater atrophy in the frontal, temporal, and parietal white matter compared with MCI patients without any neuropsychiatric symptoms. These regions of increased atrophy may represent shared white matter mechanisms and indicate a greater severity or faster progression of AD pathology. Findings from this study lend further support to the hypothesis that depression may be a symptom of prodromal AD and thus may be useful as a surrogate clinical marker to identify those MCI subjects who are most likely to progress to AD.

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