

Longitudinal pattern of regional brain volume change differentiates normal aging from MCI

I. Driscoll, PhD
C. Davatzikos, PhD
Y. An, MS
X. Wu, MS
D. Shen, PhD
M. Kraut, MD, PhD
S.M. Resnick, PhD

Address correspondence and reprint requests to Dr. Susan Resnick, LPC/GRC/NIA, 5600 Nathan Shock Dr., Baltimore, MD 21224
resnicks@mail.nih.gov

ABSTRACT

Background: Neuroimaging measures have potential as surrogate markers of disease through identification of consistent features that occur prior to clinical symptoms. Despite numerous investigations, especially in relation to the transition to clinical impairment, the regional pattern of brain changes in clinically normal older adults has not been established. We predict that the regions that show early pathologic changes in association with Alzheimer disease will show accelerated volume loss in mild cognitive impairment (MCI) compared to normal aging.

Methods: Through the Baltimore Longitudinal Study of Aging, we prospectively evaluated 138 nondemented individuals (age 64–86 years) annually for up to 10 consecutive years. Eighteen participants were diagnosed with MCI over the course of the study. Mixed-effects regression was used to compare regional brain volume trajectories of clinically normal individuals to those with MCI based on a total of 1,017 observations.

Results: All investigated volumes declined with normal aging ($p < 0.05$). Accelerated change with age was observed for ventricular CSF (vCSF), frontal gray matter, superior, middle, and medial frontal, and superior parietal regions ($p \leq 0.04$). The MCI group showed accelerated changes compared to normal controls in whole brain volume, vCSF, temporal gray matter, and orbitofrontal and temporal association cortices, including the hippocampus ($p \leq 0.04$).

Conclusion: Although age-related regional volume loss is apparent and widespread in nondemented individuals, mild cognitive impairment is associated with a unique pattern of structural vulnerability reflected in differential volume loss in specific regions. Early identification of patterns of abnormality is of fundamental importance for detecting disease onset and tracking progression. *Neurology*® 2009;72:1906–1913

GLOSSARY

AD = Alzheimer disease; **BIMC** = Blessed Information Memory Concentration Scale; **BLSA** = Baltimore Longitudinal Study of Aging; **GM** = gray matter; **ICV** = intracranial volume; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **vCSF** = ventricular CSF; **WM** = white matter.

MRI-based volume measurements have been proposed as potential surrogate markers for disease diagnosis or progression and may be particularly useful in early detection of Alzheimer disease (AD).^{1,2} Before rational approaches to diagnosis and treatment can be developed, it is essential to characterize the brains of clinically normal individuals as part of the normal developmental process and as distinct from explicit disease or pathology. It is now well-accepted that even normally aging brains undergo structural changes in the absence of neurodegenerative disease.³ A recent summary of structural brain aging indicates considerable expansion of CSF-filled cavities, mild shrinkage of brain parenchyma, and a pattern of regional changes where association cortices, the neostriatum, the hippocampus, and the cerebellum appear most sensitive to age-related volume loss.⁴

From the Laboratory of Personality and Cognition (I.D., Y.A., S.M.R.), National Institute on Aging, Baltimore, MD; Department of Radiology (C.D., X.W., D.S.), University of Pennsylvania, Philadelphia; and Department of Radiology (M.K.), Johns Hopkins Medical Institutions, Baltimore. Supported in part by NIH funding sources N01-AG-3-2124 and R01-AG14971 and by the Intramural Research Program of the NIH, National Institute on Aging.

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The majority of investigations of age effects on brain volumes are derived from cross-sectional studies,⁴ which are inherently unable to distinguish between secular and age-related changes. Longitudinal studies of brain morphology are few and vary widely in participant selection, methods, and the number of brain regions examined.^{4–8} Many use only two assessments separated by varying amounts of time to calculate mean rates of change, which essentially restricts conclusions to linear effects and overlooks individual differences. Moreover, age-based normative volume data for smaller brain regions still remain largely unavailable due to considerable methodologic variability between the studies.⁹

To better understand both global and regional changes in brain structure in later life and pathology-related divergence from normal trajectories of age-related volume decline, we investigated a community-dwelling sample of 138 older adults, including 18 individuals diagnosed with mild cognitive impairment (MCI) during the course of the study. Participants were prospectively followed for up to 10 years through the neuroimaging substudy of the Baltimore Longitudinal Study of Aging (BLSA).^{10,11} First, we characterize the trajectories of volume loss in older adults who remain clinically normal to establish a solid foundation against which pathologic changes can be compared. Second, we ask whether trajectories of tissue loss distinguish between clinically normal individuals and those with MCI. We predict that regions that show early pathologic changes in association with AD, including frontal, temporal, and parietal association cortices, will show accelerated volume loss in MCI compared to normal aging.

METHODS Participants. The sample includes 138 participants (ages 64–86 years, 90% Caucasian) who were free of dementia at initial evaluation and were prospectively followed annually for up to 10 years. Eighteen of 138 were diagnosed with MCI over the course of the study and 5 of those 18 went on to develop dementia. The sample was divided into two groups for analytic purposes, normal ($n = 120$) and MCI ($n = 18$), based on standardized diagnostic procedures for the BLSA¹² using Petersen criteria for MCI.¹³ Only participants with stable MCI diagnosis (i.e., did not revert back to normal in subsequent years) were included in the MCI group. Data points at and following dementia diagnosis were excluded; all other magnetic resonance scans were analyzed for a total of 1,017 observations. All participants were in generally good health at entrance with exclusionary

criteria encompassing CNS disease, severe cardiovascular disease, severe pulmonary disease, or metastatic cancer. Analyses were restricted to participants without current depression. Approximately half of the sample was hypertensive, the majority of which was controlled with medication. The proportion of treated individuals was similar across the two groups. Sample characteristics, functional status measures at baseline imaging evaluation, and the number of participants at each follow-up are presented in table 1. The study was approved by the local institutional review boards, and all participants gave written informed consent prior to each assessment.

BLSA participants undergo neuropsychological testing, a neurologic examination, interval medical history, medication review, and a structured informant and subject interview at each visit, the details of which have been summarized elsewhere.^{12,14} Briefly, a battery of neuropsychological tests assessing five different cognitive domains includes the following: 1) memory—California Verbal Learning Test¹⁵ and Benton Visual Retention Test¹⁶; 2) word knowledge—Primary Mental Abilities Vocabulary¹⁷; 3) attention—Digits Forward¹⁸ and the Trail Making Test-A¹⁹; 4) executive function—Digits Backward,¹⁸ Trail Making Test-B,¹⁹ and Verbal Fluency²⁰; and 5) visuospatial abilities—the Card Rotations Test.²¹

MRI acquisition. Scanning was performed on a GE Signa 1.5T scanner (Milwaukee, WI) using a high-resolution volumetric spoiled-grass axial series (repetition time = 35 msec, echo time = 5 msec, field of view = 24 cm, flip angle = 45°, matrix = 256 × 256, number of excitations = 1, voxel dimensions 0.94 × 0.94 × 1.5 mm).

MRI analysis. Image processing procedures have been previously validated and described.^{11,22,23} Briefly, images are corrected for head tilt and rotation, and reformatted parallel to the anterior-posterior commissure plane. Extracranial tissue is removed using a semiautomated procedure followed by manual editing. Next, images are segmented into white matter (WM), gray matter (GM), and CSF. The final step involves stereotaxic normalization and tissue quantitation for specific regions of interest. A template-based deformation approach is employed, using the ICBM standard MRI (Montreal Neurologic Institute) as the template and a hierarchical elastic matching algorithm for deformation and regions of interest determination²⁴; all images are normalized individually to the same template. Voxel-based analysis utilizes our RAVENS approach (regional analysis of volumes examined in normalized space),²³ whereby local values of tissue density maps (one for GM, one for WM, and one for CSF) reflect the amount of respective tissue in the vicinity of a voxel. Tissue densities are mathematical quantities measuring local tissue volumes and do not reflect any microstructural physical density of brain tissue. Intracranial volume (ICV) is determined using the template warping algorithm modified for head image registration. First, the ICV in the template is manually and carefully delineated by an expert. Then, the template with its ICV mask is warped to the space of each individual head. Finally, the warped ICV mask of template is used to directly extract the ICV of the individual. ICV at initial imaging evaluation is used for statistical adjustment to avoid potential biases of brain atrophy and partial volume effects on estimation of ICV.²⁵

Statistical analyses. Pairwise multiple comparisons with Tukey adjustments were carried out to compare sample characteristics presented in table 1. The outliers were assessed both by examining the data plots and by statistical methods. We performed Cook's *D* influence diagnostics for each brain region.

	Normal	MCI	Total sample
No.	120	18	138
Sex (male/female)	73/47	11/7	84/54
Race (white/nonwhite)	107/13	18/0	125/13
Age, y*			
Mean (SD)	70.58 (6.11)	77.26 (7.08)	71.45 (6.62)
Range	64–86	64–85	64–86
Education, y, mean (SD)	16.33 (2.74)	15.83 (3.59)	16.26 (2.85)
Range	8–20	8–20	8–20
Hypertension, n (%)	68 (52)	10 (56)	78 (52)
Follow-up, y, mean (SD)	6.02 (2.91)	5.32 (2.46)	5.92 (2.86)
Range	1–10	1–9	1–10
MMSE, mean (SD)*	28.76 (1.52)	27.47 (2.40)	28.59 (1.71)
BIMC, mean (SD)*	0.87 (1.10)	2.11 (2.17)	1.14 (1.35)
No. of scans			
Year 1	130	18	148
Year 2	117	15	132
Year 3	112	16	128
Year 4	102	14	116
Year 5	105	11	116
Year 6	97	10	107
Year 7	88	9	97
Year 8	84	6	90
Year 9	66	3	69
Year 10	14	0	14
Total scans	915	102	1,017

*Characteristics that are significantly different between the two groups: baseline age ($t_{147} = 4.53$; $p < 0.001$) and BIMC scores ($t_{18} = 2.21$; $p = 0.04$) were higher and MMSE scores ($t_{17} = 2.48$; $p = 0.02$) lower for the MCI group. MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination (total score); BIMC = Blessed Information Memory Concentration Scale (total score).

Observations with Cook's $D > 0.01$ fell outside of the acceptable range of values and were excluded from analyses. The determination of outliers was conducted separately for each region of interest; hence the exact number of exclusions varies by brain region. On average, eight data points (range 2–18) per region were excluded from analyses, and the number of outliers generally did not seem to systematically differ between the two groups. In most cases, an individual's value was excluded for only a single year for a particular region. A total of 1,017 observations entered the analyses, after the exclusions.

Longitudinal changes were examined employing linear mixed models, which account for the correlations for repeated measures (SAS v. 9.1; SAS Institute Inc., Cary, NC). Linear mixed models (SAS PROC MIXED) were fit based on absolute regional volume measurements covarying for ICV. Age (at which the dependent measures were taken) was treated as continuous covariate and was centered on the mean to reduce multicollinearity. The full model included diagnosis (normal vs MCI), intercept, ICV, sex, age, age², and their interactions as fixed effects, and intercept, age, and age² as random effects. Sex (male, female) and clinical diagnosis (MCI, normal) were treated as class variables. Model reduction began with tests of the random effects

(using mixture χ^2 tests) and continued for fixed effects after determination of the final random effects for the model. For fixed effects, we used a backward elimination procedure based on t test and likelihood ratio tests. Nonsignificant higher order terms were deleted sequentially from the model. Annual rates of change were estimated from the linear components of the mixed regression models. The data points for the MCI group start at age 64 years; hence we restricted the analysis to those participants in the normal group with observations starting at age 64 years and older.

RESULTS Sample characteristics. The two groups were similar in demographic characteristics (see table 1), with the exception of the MCI group being nearly 7 years older at baseline ($t_{147} = 4.53$, $p < 0.001$). Mental status scores at baseline also differed between the two groups. The MCI group had a lower mean Mini-Mental State Examination (MMSE)²⁶ score ($t_{17.2} = 2.48$; $p = 0.02$) and a higher Blessed Information Memory Concentration Scale (BIMC)²⁷ score ($t_{18.4} = 2.21$; $p = 0.04$), reflecting poorer performance.

Stability measures. Stability measures for volumes across follow-up assessments indicated that measurements generally were consistent over time. Only regions with stability measures above 0.85 were included in analyses with the exception of following select regions which are important for tests of our hypotheses: superior frontal (0.75), postcentral (0.80), supramarginal (0.82), and parahippocampal (0.80) gyrus, entorhinal (0.73) and perirhinal (0.80) cortices, cuneus (0.82) and occipital regions (range 0.72–0.82).

Longitudinal brain volume change. Results are reported as significant if $p \leq 0.05$, although with Bonferroni correction for multiple comparisons, results would be considered significant at $p \leq 0.0013$.

Mixed-model results for global and regional volumes are summarized in tables 2 and 3. All regions investigated showed significant longitudinal decline in tissue volumes and increases in vCSF in clinically normal individuals. A number of regions showed nonlinear changes within the context of normal aging (i.e., accelerated atrophy with age indicated by the age² term), including vCSF ($t_{661} = 4.20$, $p < 0.001$), frontal GM ($t_{652} = -3.09$, $p = 0.002$), superior ($t_{655} = -2.97$, $p = 0.003$), middle ($t_{656} = -2.45$, $p = 0.01$), and medial ($t_{655} = -2.08$, $p = 0.04$) frontal, and superior parietal ($t_{648} = -2.79$, $p = 0.005$) regions. Sex differences in rates of normal age-related decline were observed for whole brain volume ($t_{652} = -2.15$, $p = 0.03$), vCSF ($t_{661} = 2.57$, $p = 0.01$), frontal GM ($t_{652} = -2.01$, $p = 0.04$), temporal ($t_{655} = -3.36$, $p < 0.001$) and parietal ($t_{656} = 2.43$, $p = 0.02$) WM, middle frontal ($t_{657} = -1.98$, $p = 0.05$) and superior parietal

Table 2 Annual rates of change in global and lobar brain volumes (cm³)

Region	Normal, mean (SE)	MCI, mean (SE)	Difference, mean (SE)	Effect size
Global measures				
Whole brain	-7.35 (0.24)*	-8.71 (0.68)*	1.36 (0.72)*	2.09
			$p = 0.04$	
vCSF	1.31 (0.08)*	1.86 (0.21)*	-0.55 (0.22)*	-2.50
			$p = 0.01$	
GM	-2.62 (0.18)*	-3.39 (0.50)*	0.77 (0.53)	1.45
WM	-4.54 (0.19)*	-4.60 (0.55)*	0.06 (0.57)	0.11
Lobar measures				
GM				
Frontal	-0.91 (0.07)*	-1.13 (0.19)*	0.22 (0.20)	1.21
Temporal	-0.44 (0.05)*	-0.98 (0.15)*	0.54 (0.16)*	3.38
			$p = 0.001$	
Parietal	-0.69 (0.04)*	-0.58 (0.12)*	-0.11 (0.13)	-0.85
Occipital	-0.36 (0.03)*	-0.50 (0.10)*	0.14 (0.11)	1.36
WM				
Frontal	-1.88 (0.08)*	-1.68 (0.24)*	-0.20 (0.25)	-0.80
Temporal	-1.56 (0.07)*	-1.56 (0.19)*	0.004 (0.19)	0.21
Parietal	-0.33 (0.05)*	-0.24 (0.13)*	-0.06 (0.14)	-0.59
Occipital	-0.16 (0.03)*	-0.03 (0.10)	-0.13 (0.11)	-1.18

Values denoted in normal and MCI columns represent significant linear effects.

* $p \leq 0.001$; * $p \leq 0.05$; * $p \leq 0.01$.

MCI = mild cognitive impairment; vCSF = ventricular CSF; GM = gray matter; WM = white matter.

($t_{649} = -2.25, p = 0.02$) cortices, and supramarginal ($t_{648} = -2.50, p = 0.01$) and parahippocampal ($t_{659} = -3.12, p = 0.02$) regions. Age-related atrophy in these regions was generally more pronounced in males, with the exception of parietal WM, where females showed greater rates of tissue loss.

The magnitudes of the estimated annual rates of change for all regions examined are presented in tables 2 and 3 to provide normative values against which pathologic changes can be compared. Trajectories of volume change over time are shown in figure 1 for total brain, vCSF, WM, GM, hippocampus, and orbitofrontal cortex. Regions that showed diverging trajectories for clinically normal individuals vs those with MCI (figure 2) include whole brain ($t_{729} = -2.09, p = 0.04$), vCSF ($t_{740} = 2.52, p = 0.01$), temporal GM ($t_{728} = -3.38, p = 0.001$), the hippocampus ($t_{741} = -2.53, p = 0.01$), orbitofrontal ($t_{728} = -2.13, p = 0.03$), middle temporal ($t_{737} = -2.57, p = 0.01$), and perirhinal ($t_{734} = -2.21, p = 0.03$) cortices.

DISCUSSION In a relatively large sample of older adults prospectively followed with serial MRI, we found widespread and diffuse tissue loss over time in

nondemented individuals. Moreover, against this background of age-related volume loss, individuals with MCI showed accelerated tissue loss in several specific brain regions.

Widespread longitudinal volume loss was observed in the brains of clinically normal individuals in all regions assessed. Our findings are largely in agreement with previous reports, with the exception of sensory-motor and visual cortices, which historically have been believed to be relatively spared by aging,^{4,28} yet show significant longitudinal volume loss in our normally aging sample at a 9-year follow-up. A number of regions, specifically frontal GM, superior, middle, and medial frontal, and superior parietal cortices, experience accelerated tissue loss and vCSF volume changes that increase exponentially with advancing age. Albeit not all regions show nonlinear changes with age in the absence of disease, inclusion of a nonlinear term in the analyses avoids underestimation of the magnitude of age-related atrophy. We postulate that accelerations in the rate of decline may become even more evident and important in the face of pathology, which would have implications for disease-altering treatments. Our findings and those of others²⁹ suggest that future studies should include nonlinear models.

Accelerated tissue loss may signify impending neurodegenerative disease in some cases,³⁰ but differential patterns of decline in our MCI group which do not necessarily overlap with regions showing accelerated loss with normal aging suggest that this is not necessarily the case. Some have argued that tissue loss reflects pathology in its early stages. Although some of our normally aging participants may go on to eventually develop dementia, the uniformity of our findings across the majority of normal older participants argues against this interpretation unless all individuals will eventually develop dementia. Thus, our data provide normative values against which pathologic changes can be compared.

Specific volumes that differentiated MCI from normal aging include whole brain volume, vCSF, temporal GM, orbitofrontal, middle temporal, and perirhinal cortices, and the hippocampus with non-significant trends observed in the middle frontal, inferior temporal, and entorhinal cortex, and the precuneus. We hypothesized that regions that show early pathologic changes in association with AD, including frontal, temporal, and parietal association cortices, would show accelerated volume loss in MCI compared to normal aging. Accelerated volume loss in the frontal and temporal regions in MCI follows the pattern of progression of neuropathologic changes as we originally hypothesized, although we did not observe accelerated atrophy in parietal associ-

Region	Normal, mean (SE)	MCI, mean (SE)	Difference, mean (SE)	Effect size
Frontal				
Superior	-0.06 (0.02)*	-0.12 (0.05)*	0.06 (0.05)	1.31
Middle	-0.29 (0.02)*	-0.40 (0.07)*	0.11 (0.07)*	1.87
<i>p</i> = 0.06				
Inferior	-0.13 (0.02)*	-0.08 (0.05)	-0.05 (0.06)	-0.80
Medial	-0.09 (0.02)*	-0.14 (0.05)*	0.04 (0.05)	0.88
Orbitofrontal	-0.06 (0.01)*	-0.15 (0.04)*	0.09 (0.04) [§]	2.13
<i>p</i> = 0.03				
Sensorimotor				
Precentral	-0.20 (0.02)*	-0.19 (0.06)*	-0.01 (0.06)	-0.17
Postcentral	-0.19 (0.02)*	-0.20 (0.06)*	0.01 (0.06)	0.21
Parietal				
Superior	-0.21 (0.02)*	-0.20 (0.05)*	-0.01 (0.05)	-0.06
Supramarginal	-0.09 (0.01)*	-0.08 (0.03)*	-0.01 (0.03)	-0.26
Angular gyrus	-0.12 (0.01)*	-0.08 (0.04)	-0.04 (0.04)	-0.89
Temporal				
Superior	-0.22 (0.02)*	-0.28 (0.05)*	0.06 (0.06)	1.12
Middle	-0.20 (0.02)*	-0.39 (0.07)*	0.19 (0.07)*	2.57
<i>p</i> = 0.01				
Inferior	-0.07 (0.01)*	-0.13 (0.03)*	0.06 (0.03)*	1.79
<i>p</i> = 0.07				
Hippocampus	-0.02 (0.003)*	-0.05 (0.01)*	0.03 (0.01)*	3.00
<i>p</i> = 0.01				
Parahippocampal	-0.01 (0.002)*	-0.02 (0.01) [§]	0.01 (0.01)	1.26
Entorhinal cortex	0.01 (0.003) [§]	-0.01 (0.01)	0.02 (0.01)*	1.89
<i>p</i> = 0.06				
Perirhinal cortex	-0.02 (0.003)*	-0.04 (0.01)*	0.02 (0.01) [§]	2.21
<i>p</i> = 0.03				
Occipital				
Superior	-0.08 (0.01)*	-0.09 (0.03)*	0.01 (0.03)	0.45
Middle	-0.06 (0.01)*	-0.08 (0.03)*	0.02 (0.03)	0.59
Inferior	-0.02 (0.01)*	-0.05 (0.02)*	0.03 (0.02)	1.40
Occipitotemporal	-0.06 (0.02)*	-0.14 (0.05)*	0.08 (0.06)	1.35
Occipital pole	-0.05 (0.01)*	-0.07 (0.02)*	0.02 (0.02)	0.92
Other regions				
Cingulate gyrus	-0.21 (0.02)*	-0.23 (0.05)*	0.02 (0.05)	0.38
Precuneus	-0.04 (0.01)*	-0.01 (0.01)	-0.03 (0.01)*	-1.85
<i>p</i> = 0.06				
Cuneus	-0.06 (0.01)*	-0.09 (0.02)*	0.03 (0.02)	1.20

Values denoted in normal and MCI columns represent significant linear effects.
 **p* ≤ 0.01; †*p* ≤ 0.001; ‡nonsignificant trend 0.05 < *p* ≤ 0.07; §*p* ≤ 0.05.
 MCI = mild cognitive impairment.

ation cortices. A word of caution is in order when interpreting the MCI differences. Our MCI sample is small compared to the normal sample, as it was limited to the participants who were diagnosed with MCI during the course of the study rather than fo-

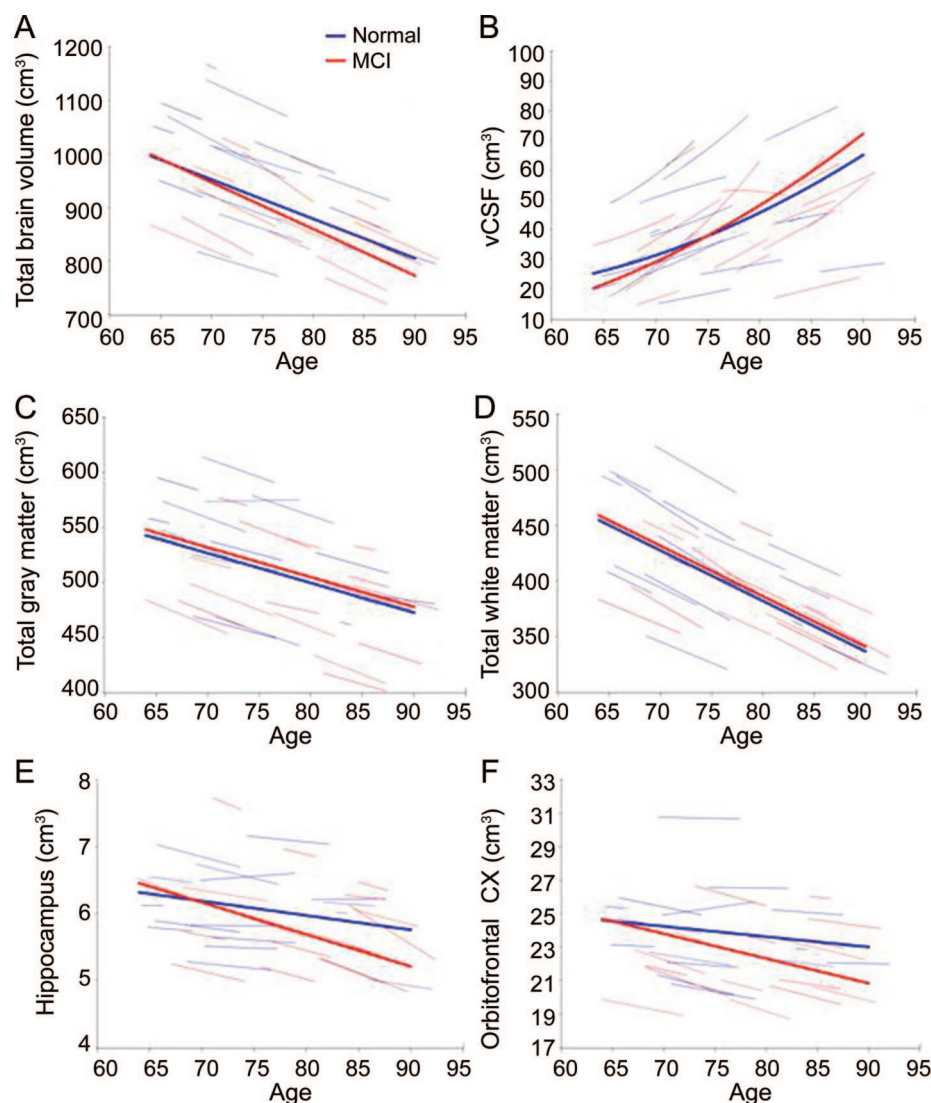
cused on a sample ascertained due to MCI status. A larger number of participants over longer intervals will be crucial in determining the sensitivity of different volume measures to MCI with greater confidence. This, however, should not undermine the unique aspects of the study, such as the large number of follow-up assessments, relatively short periods between assessments, and the extensive characterization of this sample.

Smaller regions, such as the hippocampus, orbito-frontal cortex, and the cingulate gyrus, are also of particular interest because these regions are affected very early in the process of AD progression.^{2,31} For example, both neuroimaging^{2,32} and neuropathologic³³ findings converge on the hippocampus as an early focus of AD pathology. Posterior cingulate cortex involvement in MCI or very early AD has been suggested with both FDG-PET³⁴ and MRI.³⁰ In our sample, the trajectories of hippocampal and orbito-frontal volume loss, but not the cingulate gyrus, discriminate between normal aging and MCI. The current volumetric analyses, however, do not discriminate the anterior from posterior cingulate region and hence may lack sensitivity to changes in specific cingulate subregions. We observed substantial overlap between the regions that exhibit pathology-related volume decline compared to those that are affected on a neuropathologic level, suggesting some shared underlying mechanisms.

The present sample is not population-based; the majority of our sample is highly educated and Caucasian. The relative homogeneity of the sample, however, may be seen as an asset because the majority of our sample has good access to medical care and has remained relatively healthy over the follow-up interval. Also, our regional definitions are based on a template brain, which may limit comparisons of volumes among regions but has less effect on interpretation of within-subject longitudinal change. These limitations, however, should not undermine the unique aspects of our study, namely a large number of elderly individuals who are prospectively followed for many years on an annual basis, extensively characterized, and studied with state-of-the-art image processing methods.

A recent report from our group demonstrated that volumes of a single region provide only limited accuracy in discriminating individuals with MCI from those who remain cognitively normal, while a 90% diagnostic accuracy in discriminating MCI from cognitively normal individuals based on a single MRI scan was achieved using computer-based high-dimensional pattern classification of multiple MRI features and spatial patterns of brain atrophy.³⁵ Our present findings suggest several regions where longitudinal trajectories of tissue loss may

Figure 1 Trajectories of select brain volume changes (cm³)



Age-related changes in (A) whole brain volume, (B) ventricular CSF (vCSF), (C) total white matter, (D) total gray matter, (E) hippocampus, and (F) orbitofrontal cortex. Thin red (mild cognitive impairment [MCI]) and blue (normal) lines represent individual volumes over time for a random sample of participants; thick red and blue lines indicate respective estimated average volumes for each group. Increase in vCSF accelerates with age. The hippocampus and orbitofrontal cortex decline linearly with increasing age and at a steeper rate in the MCI group. Males show steeper changes in whole brain and vCSF volume decline.

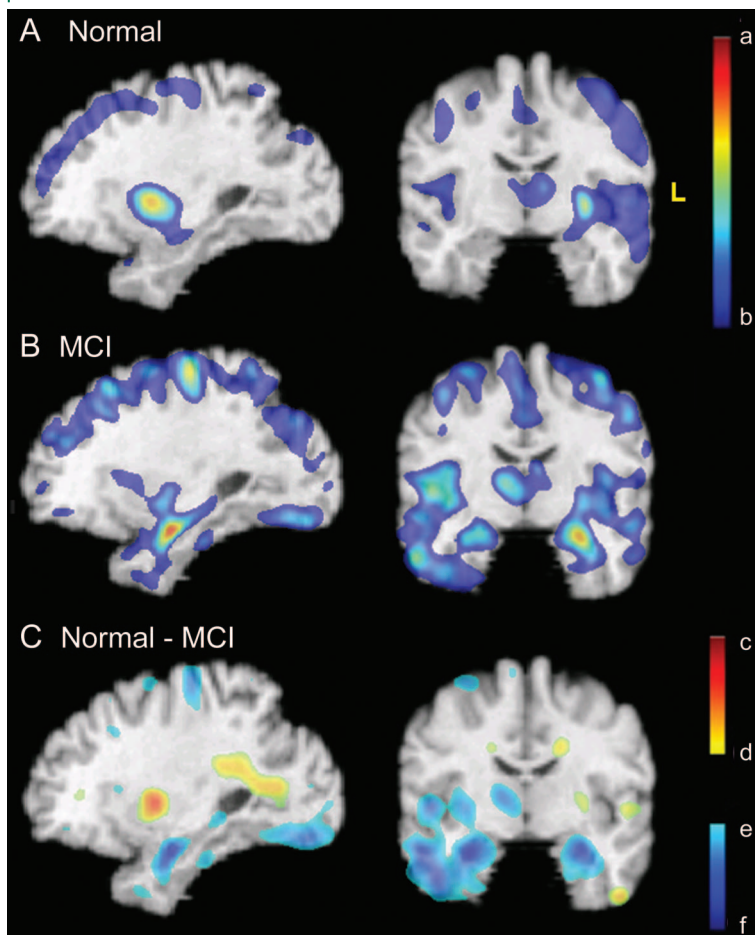
further enhance early detection. Defining the pattern and rate of longitudinal brain changes would be particularly pertinent when monitoring therapeutic responses or when predicting the onset of a neurodegenerative illness.

Overall, we identified regions with differential rates of tissue loss that distinguish between cognitively impaired and unimpaired individuals and provided normative values against which pathologic changes can be compared. Our current data allow us to begin to understand the pathologic progression and address the limitations of previous studies imposed by shorter follow-up intervals. Furthermore, our longitudinal model enables us to compare the trajectories of change in a normal aging population

to a group of individuals who transitioned to cognitive impairment and our longer follow-up interval provides greater power for detection of nonlinear age changes. Identification of differential rates of early changes has direct implications for the utility of MRI as a surrogate marker of AD and suggests a new window of opportunity for preventive strategies.

In addition to confirming some aspects of existing cross-sectional and longitudinal findings of normal and MCI-related changes in brain volume,⁹ our findings extend them by providing information on both global and localized longitudinal changes, many of which have not been investigated previously. Our findings serve as bases for future investigations of factors that may modulate the complexities of brain at-

Figure 2 Patterns of gray matter volume loss in MCI and normal aging



Average slopes of RAVENS maps for normal (A) and MCI (B) groups. The red-yellow color indicates greater volume loss. Bottom row: Difference between the two groups: blue/green are regions in which MCI subjects showed higher rate of gray matter decrease. (C) Red/yellow colors reflect an increase of periventricular small vessel disease, which appears gray in T1-weighted images and is segmented as gray matter. The color bars display estimated regression coefficients and are defined by the following numbers, all in mm^3/year (per voxel in the template space): a = -0.020 , b = -0.0053 , c = 0.026 , d = 0.0053 , e = -0.0053 , f = -0.023 . MCI = mild cognitive impairment.

rophy trajectories. Longitudinal studies will be imperative in determining the clinical relevance of observed brain changes and their relationship to age-related cognitive decline and neuropathologic observations. As such, our and other longitudinal MRI studies can help better direct neuropathologic studies, which are critical in elucidating the cellular basis of the in vivo imaging findings. Suitable animal models using both neuroimaging and histologic tools and neuropathologic assessments of humans followed longitudinally also may be helpful in elucidating the biologic meaning of regional brain shrinkage.

AUTHOR CONTRIBUTIONS

Y. An conducted the statistical analysis.

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