Regional Brain Atrophy Rate Predicts Future Cognitive Decline: 6-year Longitudinal MR Imaging Study of Normal Aging

PURPOSE: To determine if medial temporal lobe (MTL) atrophy rate, assessed by using an automated procedure over the initial time interval of a 6-year, three-time-point longitudinal study, is predictive of future memory decline.

MATERIALS AND METHODS: Healthy elderly subjects (age, >60 years) were administered a comprehensive battery of neuropsychometric tests and underwent magnetic resonance (MR) imaging at baseline and two or more follow-up examinations. The rate of brain atrophy between the baseline and first follow-up examinations was assessed by using an automated procedure that included spatial coregistration of the two images and regional brain boundary shift analysis. At final observation, the 45 subjects were separated into a group of those who did and a group of those who did not show objective evidence of cognitive decline. A forward stepwise logistic regression model was used to identify variables that predicted decline.

RESULTS: Thirty-two subjects remained healthy, and 13 showed cognitive decline. Among subjects who showed cognitive decline, six declined after the second observation. MTL atrophy rate, through its interactions with sex and age, was the most significant predictor of decline. The overall accuracy of prediction was 89% (in 40 of 45 subjects), with 91% specificity (in 29 of 32 subjects) and 85% sensitivity (in 11 of 13 subjects).

CONCLUSION: Among healthy elderly individuals, increased MTL atrophy rate appears to be predictive of future memory decline.

Many healthy elderly individuals are at risk for memory impairment, one of the most disturbing aspects of aging (1). When these amnesic changes are first clinically recognizable, they are often referred to as mild cognitive impairment (MCI) (2). MCI increases the risk of future Alzheimer disease (AD) and is often diagnosed at pathologic examination as AD (3). Individuals with MCI decline to dementia at an annual rate of 10%–15%, as compared with a rate of 1%–2% among healthy elderly individuals (2,4,5). Several behavioral and anatomic predictors of the decline from MCI to AD have been reported. However, transition from normal aging to MCI is largely uncharted.

The results of cross-sectional structural imaging studies consistently show increased vulnerability of the medial temporal lobe (MTL) structures in normal aging and in very mild AD (6–14). There are several cross-sectional observations correlating baseline hippocampal size with memory task performance in healthy elderly individuals (15–17). However, limited longitudinal data describing the predictive value of these relationships exist. In unaffected subjects genetically at risk for early-onset AD, whole-brain atrophy measured at magnetic resonance (MR) imaging was predictive of decline to AD (18,19). Results of a recent study with positron emission tomography (PET) showed that in healthy elderly individuals, reduced metabolism in the entorhinal cortex is predictive of decline to MCI (20).
The purpose of our MR imaging study was to determine if MTL atrophy rate, assessed by using an automated procedure over the initial 2-year interval of a 6-year, three-time-point longitudinal study, is predictive of future memory decline.

MATERIALS AND METHODS

Subjects

Subjects were community-residing volunteers who responded to advertisements or were spouses and/or caregivers of patients with dementia who were being evaluated in our AD Core Center. Fifty-five high-functioning healthy elderly individuals were recruited. All were high school graduates, and 42 (76%) had education beyond high school. Subjects signed informed consent forms, were administered an extensive battery of screening and diagnostic tests at baseline, and were scheduled for a series of follow-up examinations every 2 years. Examinations included medical, neurologic, psychiatric, and family history assessments; APOE genotyping; MR imaging; and a comprehensive battery of neuropsychometric tests. The study was approved by our institutional research board. At least three observations were performed for all subjects, with 21 subjects (47%) undergoing four or more observations. These observations were, on the average, 2.2 years apart.

The measures used to assess cognition and memory included the following: the Global Deterioration Scale (GDS), with scoring performed on the basis of results of extensive clinical interviews (21,22); the Mini-Mental State Examination (MMSE) (23); and the Guild Memory Test (24), which included immediate and delayed recall of paragraphs, verbal and visual paired associates, digits-forward-and-backward testing, digit symbol substitution, and a vocabulary test. Also used were tests of a shopping list, visual recognition memory, confrontation naming, and delayed spatial recall (4).

Baseline selection criteria were GDS score of 2 or lower, MMSE score of 28 or greater, age of 60 years or older, no contraindications to MR imaging, absence of gross brain abnormalities, and no evidence of neurologic, medical, or psychiatric conditions that could affect cognition. At baseline, all subjects were free of clinically detected cognitive impairment in memory, concentration, orientation, language, executive function, and activities of daily life.

Definition of Cognitive Decline

Subjects were prospectively followed up for 6 years to ascertain which subjects remained cognitively healthy and which subjects experienced decline. Decline to MCI was defined by using guidelines similar to those advocated by Petersen and colleagues at the Mayo Clinic (2,25,26). MCI was defined by the following: (a) a GDS score of 3, indicating a decline in functioning (including memory complaints) corroborated by an informant and determined by the examining physician; (b) objective memory impairments, as demonstrated by a neuropsychologic memory test score that was 1.5 SD below that of healthy elderly individuals of matching age, sex, and education; and (c) the subject not meeting criteria for dementia. The statistical distribution of the memory test scores required in point b was derived from a database of 282 longitudinal observations of healthy subjects 60–87 years of age. The diagnosis of AD was rendered according to generally accepted clinical criteria (27).

Serial MR Imaging Examinations

Serial MR imaging examinations were performed in all subjects. Among the 55 high-functioning healthy elderly individuals recruited, 45 successfully completed the second examination within 40 months after the first examination and formed the study cohort. The majority of the included subjects (ie, 35 [78%] of 45) underwent a second MR imaging examination within 20–28 months of the baseline examination, while three subjects (7%) were reexamined with MR imaging at 6–19 months and seven subjects (16%) were reexamined at 29–40 months. Three-dimensional T1-weighted MR imaging was performed with a 1.5-T MR imaging unit (Signa; GE Medical Systems, Milwaukee, Wis) by using a spoiled gradient-recalled acquisition in the steady state sequence with the following acquisition parameters: repetition time msec/echo time msec, 35/9; number of signals acquired, one; flip angle, 60°; acquisition matrix, 256 × 192; section thickness, 1.3 mm; field of view, 18 cm; and 124 contiguous coronal sections.

Coregistration

Analysis was performed with the observers blinded to all clinical data. The interhemispheric plane was determined on the basis of landmarks and was defined as the yz plane. Voxels outside the brain were automatically isolated from the brain mask K. The set K was constructed as the largest contiguous structure that is only weakly connected to adjacent structures (eg, optic nerve connection to the eyes). A cost function C reflecting the similarity of the baseline and the follow-up images within K was then evaluated (28). The rigid-body spatial transformation that minimizes C was used to produce registered images. Trilinear interpolation was used to compute C during minimization. Anisotropic voxel size was taken into account mathematically, without interpolation to cubic voxels. Upon convergence, the images were resampled by using sinc interpolation. Biases were avoided by resampling both baseline and follow-up images exactly once. The coregistration process takes 20–30 minutes, it does not require an expert observer, and is capable of subvoxel accuracy. One author (D.F.) performed the coregistrations.

Definition of the MTL Region

A box-shaped bilateral MTL region of interest (ROI) was generated by using simple criteria. Horizontal and vertical box sizes were defined as 0.25 times the left-to-right and craniocaudal dimensions of the cranial cavity. The anterior plane was defined by the anteriormost appearance of the pes hippocampus, and the posterior plane was defined by the anterior crux of the fornix. The operator presented with the coronal image located midway between these two planes. The operator then selected the centers of the left and the right hippocampus with a mouse click, and these centers became the centers of the left and the right MTL boxes. The “whole-brain” ROI was generated automatically by extending the brain parenchyma by 2.1 mm outward. The MTL ROIs were generated by one author (D.F.), and, for each case, their locations were verified by at least two coauthors.

To test how mispositioning of the box affects the atrophy measurements, each coordinate that defined the MTL box was subject to a random ±4-mm perturbation. For each of the 45 study subjects, the original and the perturbed regions were analyzed, and the two results were tested for agreement (29).

Estimation of Atrophy

According to the approach of Freeborough et al (30) and Fox and Freeborough (31), volumetric analyses were performed by “decomposing” the brain volume into...
its interior $E$ and border $B$ components. In the first step, a set $M$ was constructed by selecting voxels at the gray level above 0.55 $W$—where $W$ is the signal intensity of the white matter—and the constant 0.55 was determined empirically by using the results of phantom studies (32). The volume $V_E$ and the mean signal intensity $S_E$ of the interior region $E$ were then computed. Brain border $B$ was constructed as a three-dimensional shell that initially spanned the baseline and the follow-up edges of the set $M$. $B$ was then extended 1.4 mm inward and 1.4 mm outward. For each voxel in $B$, we determined the partial tissue decomposition by using a two-compartment model (33,34). Assuming that only the brain and cerebrospinal fluid (CSF) contribute to the signal intensity $s$, we have

$$b + c = v$$

(1)

and

$$bS_E + cS_c = s,$$

(2)

where $v$ is the voxel volume; $b$ and $c$ are the partial volumes of the brain and CSF, respectively, within the voxel; and $S_c$ denotes the signal intensity of CSF. Equations (1) and (2) are solved for $b$ and $c$, and then these values are integrated over the entire three-dimensional ROI. It should be noted that values $S_E$ and $S_c$ may vary across brain regions owing to nonuniformities in the MR signal. $S_c$ is computed with the following equation:

$$S_c = rS_E,$$

(3)

where $r$ is the contrast between CSF and the brain parenchyma, which is assumed to be constant across brain regions. The value $r = 0.32$ for the T1-weighted MR imaging sequence we used was determined on the basis of results of phantom studies and from reference T1 values for mature brain tissue at 1.5 T (35). The average T1 value of the cerebral gray and white matter was used ($T1 = 820$ msec). Because the MR imaging unit and imaging sequence were not changed during the study period, $r$ was assumed to be a constant.

The annual atrophy rate in each ROI was expressed as $(V_b - V_f)/(V_b \Delta t)$, where $V_b$ is the baseline brain ROI volume, $V_f$ is the follow-up brain ROI volume, and $\Delta t$ is the time between the two MR imaging examinations.

**Statistical Analysis**

Logistic regression was used to construct a model relating the clinical outcome (ie, decline or no decline) and the following independent variables: age at baseline, years of education, sex, whole-brain and MTL atrophy at baseline, and whole-brain and MTL atrophy rates (in terms of percentages per year). After examining the main effects, we included the interaction terms. A forward stepwise selection mode (SPSS for Windows, version 10.0; SPSS, Chicago, Ill) was used, with iterative entry of variables based on test score $P$ values of less than .05 and removal of variables based on likelihood ratio statistics with a probability of .10. For each variable in the model, we examined the coefficient, standard error of the coefficient, estimated odds ratio, and 95% CI.

**RESULTS**

Tables 1 and 2 provide the demographic descriptions and the distributions of measured neuroimaging variables at baseline and at the end of year 2. After an average of 6.1 years of observations, 32 subjects remained healthy and 13 declined and received a diagnosis of MCI ($n = 9$) or mild to severe AD ($n = 4$). Declining subjects were found to be, on the average, 5 years older than those who did not decline, but did not differ in education level, sex, or APOE genotype. Of the 13 subjects who declined, seven declined before and six declined after the first follow-up interval. Examination of the medical records and MR imaging findings revealed that none of the declining subjects had experienced any neurologic, medical, or psychologic event that could account for the observed decline.

Figure 1 shows plots of annual atrophy rates in all subjects versus their age at baseline. Figure 2 illustrates three individual cases.

At testing for main effects, MTL atrophy rate was found to be the only significant predictor of decline in the regression model. The overall accuracy of prediction was 89% (in 40 of 45 subjects; 95% CI: 80%, 98%), with 91% specificity (in 29 of 32 subjects; 95% CI: 81%, 100%) and 85% sensitivity (in 11 of 13 subjects; 95% CI: 65%, 100%). The annual MTL atrophy rate of 0.7% best enabled the separation of declining from nondeclining subjects. The odds ratio for cognitive decline was 1.7 (95% CI: 1.2, 2.3) for each 0.1% per year of MTL atrophy rate as a risk factor. When interaction terms were included in the model, the interaction between MTL atrophy rate and age and the interaction between MTL atrophy rate and sex were the only two predictors of decline (Table 2).

The regression model based on demographic and psychometric scores, including baseline and first follow-up MMSE scores, achieved 76% accuracy (in 34 of 45 subjects; 95% CI: 63%, 88%). Adding MTL atrophy rate to this regression model significantly improved the classification ($P < .001$, $\chi^2$ test). Without the

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**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects ($n = 45$)</th>
<th>Subjects with Continued Health ($n = 32$)</th>
<th>Subjects with Cognitive Decline ($n = 13$)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex†</td>
<td></td>
<td></td>
<td></td>
<td>.19</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>20</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Percentage female</td>
<td>56</td>
<td>62</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Education ($y$)‡</td>
<td>15.5 ± 2.3</td>
<td>15.7 ± 2.5</td>
<td>14.9 ± 1.9</td>
<td>.32</td>
</tr>
<tr>
<td>Age at baseline ($y$)‡</td>
<td>69.8 ± 5.4</td>
<td>68.2 ± 5.1</td>
<td>73.6 ± 4.1</td>
<td>.002</td>
</tr>
<tr>
<td>APOE genotype†</td>
<td></td>
<td></td>
<td></td>
<td>.33</td>
</tr>
<tr>
<td>E4+</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Percentage E4+</td>
<td>34</td>
<td>25</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>GDS score‡</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.91 ± 0.36</td>
<td>1.88 ± 0.42</td>
<td>2.00 ± 0.00</td>
<td>.10</td>
</tr>
<tr>
<td>Year 2</td>
<td>2.40 ± 0.47</td>
<td>2.09 ± 0.47</td>
<td>3.15 ± 0.90</td>
<td>.001</td>
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<tr>
<td>MMSE score†</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29.1 ± 1.0</td>
<td>29.2 ± 1.1</td>
<td>29.0 ± 0.8</td>
<td>.59</td>
</tr>
<tr>
<td>Year 2</td>
<td>28.5 ± 1.9</td>
<td>29.0 ± 1.2</td>
<td>27.1 ± 2.5</td>
<td>.02</td>
</tr>
</tbody>
</table>

* $P$ values for differences between declining and nondeclining subject groups were calculated with the Fisher exact test for sex and APOE genotype and with the t test for all other variables.

† Unless otherwise indicated, data are numbers of subjects with the given characteristic.

‡ Unless otherwise indicated, data are mean values ± SDs.
seven subjects who declined before the second MR imaging examination, the prediction model yielded essentially the same result: The MTL atrophy rate interactions with age and sex significantly predicted decline, with an accuracy of 89% (in 34 of 38 subjects; 95% CI: 80%, 99%).

Positioning sensitivity analysis results indicated that a random ±4-mm error in position of the MTL box introduced a relatively minor error (1 SD = 0.05%/y) in atrophy rate (Fig 3). The difference between the original and perturbed results did not correlate with atrophy rates (R = 0.03, P = .88).

**DISCUSSION**

**Relationship of Current to Previous Findings**

Braak and Braak (36) reported the presence of neurofibrillary tangles in the hippocampus and entorhinal cortex in elderly control subjects at postmortem examination and more extensive MTL changes in subjects with mild memory impairment. Results of recent work by Morris et al (3) indicate that patients with MCI often show AD-related findings in the MTL at neuropathologic examination. Our results provide longitudinal data compatible with this view.

To our knowledge, increased rates of MTL atrophy in healthy geriatric subjects prior to decline to MCI or AD is a new finding. Fluid registration of serial MR imaging examinations was used to demonstrate a significant rate of hippocampal volume loss in four presymptomatic individuals (mean age, 43.3) at risk of familial AD who were followed up to the diagnosis of AD (37). We are not aware of any other three-time-point study in which atrophy rate in the initial time interval, prior to the subsequent diagnosis of MCI or AD, was measured.

In a two-time-point follow-up study, Jack et al (38) measured hippocampal volumes in 58 healthy control subjects who underwent two MR imaging examinations separated by 3 years. A significant difference in hippocampal annual atrophy rate was observed between 48 stable control subjects (1.7% ± 0.9) and 10 subjects who declined to MCI or AD (2.8% ± 1.7). The larger magnitude of atrophy rates observed by Jack et al may have been due to the significantly more advanced age of their subjects (average age, 81 years) compared with an average age of 70 years in our cohort. There were also differences in the length of the observation period and in the brain structures measured; our geometrically defined region contained a large number of brain structures that extend beyond the hippocampus.

The value of 0.58% per year for the whole-brain atrophy rates we observed in nondelining individuals is comparable with the corresponding value of 0.4% per year measured by Fox et al in their younger (mean age, 55 years) control subjects (39,40). Moreover, there is consistency between the average whole-brain atrophy rate of 1.3% per year that we observed in declining elderly subjects and the rate of 2.4% that Fox et al reported for patients with AD (39).

Our study incorporated the highly sensitive boundary shift algorithm of Freeborough et al (30) and Fox and Freeborough (31). To our knowledge, our article is the first to describe the use of this method on a regional basis. Moreover, to our knowledge, our study is the first to apply the method to the prediction of conversion from normal values to MCI. The regional implementation of the method potentially makes the computations less sensitive to MR image nonuniformities than the whole-brain approach. Moreover, explicit inclusion of the value r in Equation (3) should, in theory, enable one to process serial images acquired by using different MR imaging sequences with different contrast between CSF and the brain in the baseline and in the follow-up MR imaging examinations. Currently, the inability to handle technologic upgrades limits the widespread use of quantitative analyses of serial MR imaging findings.

Because of the recent characterization of MCI as a condition, there are few data on the incidence of MCI. The patients in our study experienced an annual incidence of conversion to MCI of 3.3% per
year [(9/45)/6 years], slightly lower than the incidence of conversion observed by Jack et al (38). It is worth noting that Jack et al used a Clinical Dementia Rating score of 0.5 rather than a GDS score of 3 as one of the three requirements for a diagnosis of MCI. No information currently exists on the relative merits of these variants in the definition of MCI.

The annual incidence of AD in our study was 1.5% [(4/45)/6 years] and is in agreement with the values reported in the published studies. It should be noted that the incidence of AD is highly age related, increasing nearly exponentially from the 6th through the 9th decades of life (41).

Limitations of the Technique

Although hippocampal atrophy has been shown to correlate strongly ($R = 0.97$) with hippocampal neuronal loss (42), it should be recognized that factors such as hydrocephalus, alcoholism, and steroids may have an effect on brain, CSF, and blood volumes. Careful screening for these confounding factors, as was performed in our study, is therefore of the essence.

Since all of our subjects were recruited at a research clinic in a metropolitan area, one should be cautious when extrapolating these findings to the general population at risk for MCI and AD.

Implications

Results of this 6-year longitudinal study revealed MTL atrophy rate to be a significant risk factor for future cognitive decline. Neither whole-brain atrophy at baseline or follow-up nor MTL atrophy at baseline or follow-up added to the predictive power of MTL atrophy rate.

A limitation of many existing studies is the dependence on ROI tracing techniques that are time consuming and susceptible to intra- and interoperator differences. Several manual, operator-dependent steps of the present procedure serve only to provide an initial approximation to the subsequent automated algorithm. The technique appears to be insensitive to small errors in locating the box-like MTL region.

Increased MTL atrophy rate appears to be predictive of an early stage of memory decline. It remains to be seen if a shorter interval between the first and the second MR imaging examinations can maintain a similar (approximately 90%) prediction accuracy while increasing the lead time between the neuroimaging-based diagnosis and the manifestation of clinically recognizable signs. Accurate and early recognition of atrophic changes could enable therapy and better tracking of the progression to MCI and early AD in an individual patient.

References

Radiology 696/H18528