Atrophy rate in medial temporal lobe during progression of Alzheimer disease

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Abstract—Objective: To establish the progression of brain atrophy rates in patients with a known date of onset of Alzheimer disease (AD). Methods: Each of 18 subjects had two high-resolution T1-weighted three-dimensional MRI examinations. The two MRIs were coregistered and the annual rate of brain tissue atrophy was derived both for the entire brain and regionally for the left and right medial temporal lobe (MTL). Time since onset (TSO) of AD, defined as the interval between the date of onset and the midpoint of MRI dates, ranged from −2.9 to 4.2 years. Results: In patients with AD, TSO was a correlate of the atrophy rate for both the left MTL ($R^2 = 0.58, p = 0.001$) and right MTL ($R^2 = 0.30, p = 0.03$). When serial measurements were applied to a control group of 21 cognitively normal elderly subjects, MTL atrophy rate classified the group membership (AD vs normal cognition) with an accuracy of 92.3%. Conclusion: Increased annual atrophy rate in the medial temporal lobe is a potential diagnostic marker of the progression of Alzheimer disease.

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Better in vivo methods for early diagnosis and estimation of Alzheimer disease (AD) progression are needed. Three promising neuroimaging correlates of AD are reduced brain blood flow and metabolism,1–3 brain atrophy measured from a single MRI,4–7 and the atrophy rate derived from serial MRIs.8–12 Measurements of global atrophy within the brain have found increased volume loss in patients with AD compared to cognitively normal subjects.4,8,9,11 However, this finding has not been specific to AD, as whole brain atrophy is found in vascular dementia,13 frontotemporal dementia,11 and even in elderly subjects without apparent cognitive decline.14 Based on histologic data that demonstrated early pathologic changes within the medial temporal lobe (MTL), in particular in the hippocampus and the entorhinal cortex,15 numerous volumetric studies have focused on MTL structures in search for markers more specific to AD.3,12,16 Nevertheless, there are limited quantitative data to describe the range of values of atrophy encountered during the onset and progression of AD.

In this study we estimate the course of brain atrophy in cases of sporadic AD with a known date of onset. We selected subjects for whom this date could be established with reasonable accuracy. Atrophy rate was assessed using serial MRI and a regional variant of a brain boundary shift integral method.17 The results support the hypothesis that brain atrophy in the MTL region follows a fairly consistent course. In particular, we provide evidence that the relative MTL atrophy rate increases in the course of the disease.

Materials and methods. Subjects. Subjects were patients in the early stage of AD being evaluated in our AD Core Center. Subjects gave written informed consent, were given an extensive screening and diagnostic battery at baseline, and were scheduled for a continuous series of follow-up examinations every 2 years. Examinations consisted of medical, neurologic, and psychiatric evaluations, a comprehensive battery of neuropsychometric tests, and a comprehensive set of MRI acquisition sequences. In order to assure the highest precision of measurement of brain change, the patients were required to undergo at least two MRI examinations in a time period P during which neither the scan protocol nor the scanner were changed (shaded area in figure 1). Independently, each patient was required to have had two consecutive examinations, one with a negative diagnosis for probable AD, and a follow-up in which the patient was first diagnosed with probable AD. Thus, we selected all subjects who satisfied the following four conditions: 1) on the initial examination the subject’s cognitive impairment did not meet the AD criteria recommended by National Institute of Neurologic Disorders and Stroke–AD and Related Disorders Association (NINDS-ADRA), 2) the subject was diagnosed with probable AD according to NINDS-ADRA on one of the follow-up examinations, 3) the subject completed at least two high-resolution MR scans during a specific 4-year period P (see below), and 4) the subject was free of MRI evidence of overt brain pathology such as tumor, stroke, hydrocephalus, or significant trauma. Also excluded were individuals with a history of alcoholism, drug abuse, or psychiatric illness, and those with physical impairment that may adversely affect the neuropsychological testing.

Among the 78 patients with AD evaluated with serial MRI in our Core Center during the 4-year study period, 18 subjects with AD (5 men and 13 women) fulfilled the four inclusion criteria. The majority of subjects with AD failed to satisfy point 1, i.e., they were given the diagnosis of probable AD on their first visit to our clinic. (Without a prior visit we could not determine the date of onset, a key variable in this study.) At the examination just prior to the examination when the AD diagnosis was made, 15 out of 18 patients (83%) qualified for the commonly used guidelines for mild cognitive impairment that require neuropsychological memory test score to be 1.5 SD below the mean score of normal elderly subjects of matching age, sex, and education.23 The statistical distribution of the memory test scores was derived from our database of 282 observations on normal subjects aged 60 to 87. Study sub-
recognition,22 and shopping list recall23 (immediate and delayed recall of the word list). In Patient C, TSO has a negative value when the baseline and follow-up MRI occurred out to a minimum of 4 years after the end of period P. Control subjects also satisfied the above criteria 3 and 4. Normal cognition in controls was defined as maintaining a rating of less than or equal to 2 on the Global Deterioration Scale20 (GDS).

To remove the bias related to variable time interval between visits, the date of AD onset was defined as the midpoint between the date of the first visits at which AD was diagnosed and the prior visit (thick arrows in figure 1). Because measurement of the atrophy rate involves two MRIs, we defined the time since onset (TSO) of AD as the interval between the date of onset and the steady state sequence. Each MRI used identical acquisition parameters: repetition time 35 msec, echo time 9 msec, number of excitations = 1, 60° flip angle, 256 × 192 acquisition matrix, 1.3 mm section thickness, 18 cm field of view, and 124 contiguous coronal slices.

Image analysis. The baseline scans were first resampled to align the yz plane with the inter-hemispheric plane and coregistered with the follow-up scan using an iterative method.26 The method is known to achieve sub-voxel accuracy. Both baseline and follow-up images were resampled exactly once using the sinc interpolation method. One author performed the coregistrations.

Annual rate of brain tissue atrophy was derived both globally for the entire brain, including the cerebellum and the pons, and regionally for the left and right MTL. The pair of coregistered images was first segmented into interior I and “border” B brain regions.11 Brain border B was constructed as a three-dimensional shell that initially spanned the baseline and the follow-up brain edges, then was extended two voxel layers inwards and two layers outwards. The interior consists of voxels within the border and the follow-up brains, but not in B. Regions of interest (ROI) R were described below were intersected with sets I and B and individually assessed for brain and CSF content at baseline and at follow-up. The mean signal of the region’s interior $R \cap I$ (the symbol $\cap$ denotes set intersection) at baseline and at follow-up were computed and used as normalization factors in all subsequent computations. Such signal normalization helps to correct for signal intensity differences that might have appeared between the follow-up scans. For each voxel in the intersection $R \cap B$, the partial volume of the brain and CSF were determined using a two-compartmental model.12 Brain volume within each region $R$ was then computed as the sum of $R \cap I$ and the partial volume of the brain in $R \cap B$.

Box-like MTL ROI were defined separately on the left and the right hemisphere. We defined the MTL box to be proportional to the subject’s premorbid brain size in order to eliminate the variability of the measurements due to differences in head sizes. The horizontal dimension was taken as one quarter of the maximum left-right dimension of the intracranial cavity. Similarly, the vertical dimension of the MTL box was equal to one quarter of the maximum cranio-caudal extent of the supratemporal space. Anterior boundary extent was guided by the appearance of the hippocampus. Specifically, the anterior boundary was defined by the posterior-most coronal slice $sa$ showing the uncal sulcus. The posterior boundary was defined by the posterior-most coronal slice $sp$ containing the tail of the hippocampus and preceding the appearance of the anterior crux of the fornix. The operator selected the mid-hippocampal slice $(sa+sp)/2$ and identified the image coordinates of the centers lc rc of the left and right hippocampus. The MTL ROIs were then generated so that their centers were positioned on the points lc and rc. The whole brain ROI W was defined as the set union (sum) $\cup B$ of the interior and the border regions.

For each of the three ROIs (right and left MTL box and the whole brain), the annual rate of atrophy $A$ was expressed as the baseline MRI ROI volume divided by the ROI volume and by the time interval between the two MRIs. The baseline atrophy was defined as the ratio of the CSF volume to the total ROI volume.

Interobserver reliability. A second observer repeated the measurements independently of the first and the agreement of the resulting measures was examined. The measurements most difficult to reproduce by two independent observers were the cranio-caudal extent of the normal temporal cavity (mean discrepancy 2.9 mm) and the location of the anterior-most plane used to define the MTL region (mean discrepancy 1.2 mm). In spite of this disagreement, the maximum discrepancy in estimating the annual MTL atrophy rate by the two observers was only 0.11% (mean absolute discrepancy 0.06%).

Statistical analysis. Linear regression models were used to evaluate the relationship between the MTL measures and the TSO, as well as the relationship between the psychometric scores and the TSO. Logistic regression model was computed to classify normal and AD subjects. SPSS (Windows version 11.0) was used for all statistical analyses. To account for the uncertainty in the date of AD onset, taken as the midpoint between the date of last clinic visit $V_1$ prior to the diagnosis, and $V_2$, the first visit at which the diagnosis was made, we have used a statistical resampling. For each case we generated a vector V of independent random variables distributed according to a uniform probability density function in the time interval $[V_1, V_2]$. Repeated
samples of vector V were used to compute the parameters and the significance of the regression model. Resampling process continued by doubling the number N of samples until the mean significance level \( P_N \) of the regression differed from the corresponding values \( P_{N/2} \) by less than 5% points, i.e., \( |P_N - P_{N/2}| < 0.05 P_N \).

**Results.** Figure 2 illustrates the baseline and coregistered follow-up MR images of three patients with AD. These images represent progressively advancing stages of AD. Multivariate linear regression model was constructed to relate the annual atrophy rate \( A \) in the left MTL, right MTL, and in the entire brain as a function of the subject’s age, sex, education level, and TSO.

TSO was a correlate of the atrophy rate for the left MTL \( (R^2 = 0.58, p < 0.001) \), right MTL \( (R^2 = 0.30, p = 0.03) \) (figure 3), and the left and right MTL combined \( (R^2 = 0.48, p = 0.001) \). Statistical resampling aimed to account for the uncertainty in the AD onset date confirmed these significance levels, with corrected \( p = 0.008 \) for the left MTL, \( p = 0.04 \) for the right MTL, and \( p = 0.005 \) for the left and right MTL combined.

In order to compare more explicitly the contribution of the left vs right MTL, we have entered these variables in permuted order using a two-block stepwise regression model. The addition of left MTL to the model containing right MTL increased \( R^2 \) by 0.256 \( (p = 0.01) \). However, right MTL did not add significant predictive power when entered to the model containing left MTL. The paired samples \( t \)-test revealed a difference between the mean atrophy levels of the two brain sides \( (1.9\%/\text{year} \text{ for right MTL vs } 2.6\%/\text{year} \text{ for the left MTL, } p = 0.05) \).

At the time of onset, atrophy rate of the entire brain was 1.4%/year, in the left MTL it was 2.2%/year, and in the right MTL 1.8%/year. There was no correlation between TSO and whole brain atrophy rate (see figure 3, \( R^2 = 0.11, p = 0.18 \)). Neither age, sex, nor education level correlated with the atrophy rates \( (p > 0.05) \).

Progression of MMSE and psychometric measures in AD. A multivariate linear regression model was used to relate the TSO with the annual changes in MMSE and psychometric tests. After covarying for subject’s age, sex, and education, stepwise addition of MMSE and psychometric test results yielded a linear model with \( R^2 = 0.40, p = 0.130 \). Only the annual change in the immediate paired associates recall test scores correlated with the TSO \( (p = 0.031) \). Nearly a third (32%) of AD subjects were unable to complete the delayed shopping list recall and the visual recognition span tests and received a zero score. The paired associates recall test also showed a large floor effect, with 30% of AD subjects receiving zero score at the baseline visit. In a three-step linear regression model we expressed TSO, a dependent variable, in terms of 1) the covariates sex, education level, and age; 2) the annual change in MMSE and in all psychometric measures; and finally 3) the annual rates of atrophy in the left MTL, right
The addition of neuroimaging measures resulted in an improvement ($R^2$ increase from 0.40 to 0.67, $p < 0.005$) and identified the left MTL atrophy rate as the sole predictor of the TSO.

Normal controls. This group consisted of 7 men and 14 women, aged 60 to 78, with mean age 67.8 ± 5.2. The annual MTL atrophy rate (both left and right sides combined) in this group was 0.37 ± 0.34%/year. There was no significant correlation between the rate of MTL atrophy and age, sex, or education level of the control subjects.

A logistic regression analysis aimed at classifying the group membership (AD vs normal control) based on the age, sex, education level, and MTL atrophy rate yielded a classification accuracy of 92.3%. Age, sex, and education did not significantly contribute to the logistic model. Only one control subject and two AD patients were incorrectly classified. The two falsely classified AD patients were imaged 2.8 to 2.9 years before the onset of AD. MTL atrophy rate was the only significant variable in the logistic regression ($p < 0.02$, OR = 1.6 for each 0.1% increase in MTL atrophy rate/year, 95% CI 1.1 to 2.2). When baseline atrophy was used instead of the atrophy rate, the classification accuracy was reduced to 76.9%.

**Discussion.** Currently, clinicians most frequently use various psychometric indices, such as the Wechsler memory scale of the Guild Memory Test or clinical measures such as the MMSE, CDR, or GDS to monitor the progression of AD and patients’ response to therapy. However, these indices have generally been considered to be coarse indicators of the status of the disease over time. Structural neuroimaging studies using MR have suggested that measures of brain atrophy may have clinical utility either as adjunct to or in place of the psychometric examinations in evaluating patients with AD. Many of the previous studies have been cross-sectional, correlating clinical symptoms with regional or whole brain atrophy measured by a single scan. Others have been longitudinal comparing the progression of atrophy as evidenced by serial MRI among cohorts with varying levels of cognitive function. Although previous studies have shown that regions of the brain of AD patients undergo atrophy more rapidly than normal elderly subjects, very few have addressed how this atrophy rate might change as the disease progresses. By categorizing subjects according to baseline diagnosis and stability of cognitive function, the rate of hippocampal atrophy was found to increase as cognitively normal subjects progress to mild cognitive impairment and AD. A recent longitudinal study examined 12 AD subjects (9 early onset AD, 3 sporadic AD, average age 47 years) with on the average of five MRIs to provide the first direct evidence of accelerated brain volume loss in the early stages of the disease.

In our group of 18 AD patients, the mean annual atrophy rate of the whole brain was 1.45%/year at the onset; the corresponding value in the MTL was 2.0%/year. Previous studies of patients with AD have reported whole brain atrophy rates of slightly higher than 2%/year. The mean MTL atrophy rate in our study is lower than what others have reported in studies involving manual tracing of various temporal lobe structures, including the hippocampus, entorhinal cortex, and the entire temporal lobe. These studies have estimated the annual atrophy rate of these brain structures to range from 3 to over 15%/year. Several factors may account for this discrepancy. Some of the prior studies were performed on subjects with familial AD, in which the pathology likely follows a different time course compared to that of the sporadic form of AD as in our subjects. Secondly, our use of geometrically defined MTL boxes may dilute the atrophy rate of more rapidly shrinking anatomic structures. Third, prior reports may have been studying subjects in more advanced stages of AD.

While there is no consensus on left/right asymme-
try of MTL atrophy in AD, the majority of cross-sectional studies confirm our observation of the left side being more vulnerable. An elastic warping technique applied to compare average gyral patterns in 26 AD patients and 20 matched controls demonstrated a greater gray matter loss in the left hemisphere of AD patients. Left hippocampus, left entorhinal cortex, and left amygdaloid body volumes were among those found to best discriminate AD from normal controls. Interestingly, the magnitude of left-to-right hippocampal asymmetry was found to increase with decreasing cognitive state. The left temporal lobe volume of AD subjects was reported to correlate strongly ($R^2 = 0.46, p = 0.0006$) with the MMSE score. In a recent magnetic resonance spectroscopy and volumetric study, the best classification of AD subjects from age-matched controls was achieved with the combination of left hippocampal N-acetylaspartate concentration and left hippocampal volume. Smaller left hippocampal volumes were significantly associated with the risk of future dementia in 115 elderly depressed but nondemented participants in a mental health clinical research center. The rate of atrophy within the whole brain did not have a statistically significant correlation with the TSO. Thus, increased rate of atrophy during the progression of AD takes place in selected brain regions rather than occurring consistently throughout the brain. This does not imply that progressive atrophy is specific to the MTL alone, as several other brain regions, including the fusiform gyrus, posterior cingulate, lateral temporoparietal, and insular cortices have been implicated.

There are few cross-sectional and no longitudinal studies comparing brain atrophy rate against individual performance in psychometric tests, and these focus on diagnostic accuracy rather than the ability to track the progression of AD. The inclusion in our study of those subjects whose MRI were taken before they were diagnosed with AD shows that the rise in atrophy rate in the MTL precedes the onset of cognitive decline. Extrapolation from our data indicates that approximately 3 years before the diagnosis of AD, the MTL atrophy rate in these subjects would have been indistinguishable from the rate of 0.3% per year seen in the normal elderly. This result is consistent with a recent estimate that the MTL volumes of patients with familial AD diverge from those of cognitively normal subjects approximately 3.5 years prior to the onset of dementia.

The increase in MTL atrophy rates for longer TSO is likely due to the increased territory of the brain affected by the disease process. Pathologic staging of AD by Braak proposes involvement of an increasingly large number of brain regions in successive stages of the disease. Annual brain loss will therefore increase even if cell death or shrinkage per unit volume proceeds at a steady rate. If this mechanism were correct, then the increase in atrophy rates will end when the entire region becomes affected by the disease. Another, methodologic explanation is based on the fact that even with a steady course of volume loss $\Delta V/\Delta t$, the atrophy rate $\Delta V/\Delta t V$ will appear to increase due to the reduction of the denominator $V$ with disease duration.

It is of interest to analyze a model of linearly increasing atrophy rates seen in figure 3. If $V(t)$ denotes the volume and $V'(t)$ its derivative as a function of time $t$ (denoted as TSO in our article), then our finding can be written as follows:

$$V'(t)/V(t) = k + q, \ t > 0, \ V(0) = V_0$$  \hspace{1cm} (1)

where $k$ is the slope and $q$ the intercept of the regression line in figure 3. The solution of equation 1 is given by a bell shaped function, which for $q = 0$ is simply

$$V(t) = V_0 e^{-kt^2}$$  \hspace{1cm} (2)

(If $q$ is not ignored, the shape of $V(t)$ does not change in a significant way.) The maximum value of $V'$ occurs at the time

$$t_{max} = 1/\sqrt{2k}$$  \hspace{1cm} (3)

Since the value of $k$ for left MTL was 0.0073/year$^2$, $t_{max} \approx 8$ years, a value that approximates an average time from the AD diagnosis to death. Thus, the model is consistent with the premise of increasing territory affected by the disease and suggests that death from AD tends to occur when the territorial spread is at its maximum.

Although the rate of MTL atrophy was measured using two MRI scans for each subject, a more direct evaluation of the relationship between the atrophy rate and the TSO would require comparing the brain at three or more times for each subject. However, such a study would require a stable MR protocol and a scanner that remains essentially unchanged over a very significant time span. The clinical utility of our study is limited by the fact that the average interval between the MRI scans was 2 years. To be useful for monitoring response to therapy, this interval would need to be shortened substantially. Further studies are warranted to assess how well the atrophy rates can be measured from scans taken at shorter intervals.

Our study demonstrates a positive linear correlation between the rate of atrophy within the MTL and the time since the clinical diagnosis of AD. Subjects who had been diagnosed with AD for a longer period showed a greater annual rate of atrophy, with an estimated overall 0.5% per year increase in the rate for each additional year the subject survives with AD. Our analysis indicates that the TSO, and not the age per se, correlates with this annual rise in the atrophy rate. A similar analysis of a control group of cognitively normal elderly confirms a small rate (averaging 0.3% per year) of MTL atrophy. It would be of interest to investigate if older age, including the eighth and the ninth decades, leads to a significant increase in the rate of atrophy in normal aging.
There is some evidence that healthy oldest-old subjects do not show greater atrophy rates than younger elderly, suggesting that large atrophic changes in older groups reflect the presence of preclinical dementia. Our finding that the atrophy rate of the MTL was able to distinguish patients with AD from a normal control group with high accuracy indicates that it may be a candidate for a diagnostic marker of AD. Although measurement of MTL atrophy rates requires serial MRIs, it has been found to be superior to single MRI measurements of brain atrophy in predicting future cognitive decline. Increasing MTL atrophy rate that is evident before the diagnosis of AD suggests that patients may be diagnosed and treated started even before the onset of cognitive decline. Second, atrophy rate may be used to monitor the progression of AD and patients’ response to therapy. Furthermore, our model of increasing MTL atrophy rates with longer TSO underscores the need for early therapy. Pharmacotherapy, even if effective in arresting further brain loss, is unlikely to improve cognitive function if sufficient tissue loss has already occurred.

References