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Rates of Hippocampal Atrophy Correlate with Change in Clinical Status in Aging and AD

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Abstract

Background—The cognitive continuum in the elderly population can be conceptually divided into those who are functioning normally (controls), those with a mild cognitive impairment (MCI), and those with probable AD.

Objectives—To test the hypothesis that the annualized rates of hippocampal atrophy differ as a function of both base-line and change in clinical group membership (control, MCI, or AD).

Methods—We identified 129 subjects from the Mayo Clinic AD Research Center/AD Patient Registry who met established criteria for normal controls, MCI, or probable AD both at entry and at the time of a subsequent clinical followup evaluation 3 ± 1 years later. Each subject underwent an MRI examination of the head at the time of the initial and at the time of the followup clinical assessment, and the annualized percentage change in hippocampal volume was computed. Controls and MCI patients could either remain cognitively stable or could decline to a lower functioning group over the period of observation.

Results—The annualized rates of hippocampal volume loss for each of the three initial clinical groups decreased progressively in the following order: AD > MC > C. Within the control and MCI groups, those who declined had a significantly greater rate of volume loss than those who remained clinically stable. The mean annualized rates of hippocampal atrophy by followup clinical group were: control-stable 1.73%, control-decliner 2.81%, MCI-stable 2.55%, MCI-decliner 3.69%, AD 3.5%.

Conclusion—Rates of hippocampal atrophy match both baseline cognitive status and the change in cognitive status over time in elderly persons who lie along the cognitive continuum from normal to MCI to AD.

Keywords

Alzheimer's Disease; MRI; Aging; Hippocampus

The transition from normal cognition to Alzheimer's disease (AD) is gradual. Patients who develop clinically evident AD pass through a transitional period during which they experience declining cognitive abilities relative to age mates. This intermediate state has been termed mild cognitive impairment (MCI) and clinical criteria for this diagnosis have been suggested (1–3). This clinically definable group is of considerable interest. This is a logical group to study for

the earliest diagnostic features of AD and is also an appropriate group in which to intervene to prevent progression to AD.

The widespread availability of magnetic resonance imaging (MRI) has increased interest in imaging as an adjunctive tool to aid in the early diagnosis of AD. This is particularly true of MRI-based measurements of medial temporal lobe atrophy, as this region is the first area of the brain involved by the neurofibrillary pathology of AD(4,5). Serial MRI studies permit calculation of rates of atrophy over time. We have previously described the rates of hippocampal atrophy in patients with a diagnosis of probable AD and a group of age and sex matched elderly controls (14 controls and 10 AD patients from that prior study are included in the current work)(6). The purpose of the current work was to extend this investigation to a larger group including individuals with MCI in order to establish the rates of hippocampal atrophy along the full memory continuum in the elderly.

Individuals recruited for this study were classified at baseline with one of the following diagnoses: control, MCI, or probable AD. In a longitudinal study such as this with two clinical assessment time points, control and MCI subjects could remain cognitively stable or could decline to a lower functioning group over the period of observation. This resulted in the designation of five clinical groups: control-stable, control-decliner, MCI-stable, MCI-decliner, and AD. The goals of this study were 1) to establish the rates of hippocampal atrophy in each of these five clinical groups, 2) to test the hypothesis that rates of hippocampal atrophy differ as a function of clinical group membership.

Patients and Methods

Recruitment and Characterization of Subjects

Patients and controls were recruited from the Mayo Alzheimer's Disease Patient Registry and Alzheimer's Disease Research Center (ADPR/ADRC) (7). These ongoing longitudinal studies of aging and dementia provide a formal mechanism for identification, enrollment, and longitudinal clinical characterization of both community and referral patients. Both the ADPR and ADRC include MRI studies. These studies were performed with Mayo IRB approval and informed consent of the subject or an appropriate proxy.

Inclusion criteria for this study were the following. Subjects must have had two ADPR/ADRC clinical assessments separated by a minimum of two and a maximum of four years. At both baseline and followup assessments the subjects must have been classified into one of three clinical groups: control, MCI, or probable AD. Out of a larger group of ADPR/ADRC subjects who participated in the ongoing longitudinal clinical/MRI studies, 129 subjects met these criteria. Potential subjects who had symptoms which were clinically felt to be unrelated to AD were excluded. For example, subjects who suffered a stroke or who developed depression before or during the followup period were excluded. The objective of this inclusion/exclusion process was to obtain a cohort of individuals who fit the profile of the cognitive continuum from normal aging to a condition which on clinical grounds was felt to most likely represent AD.

Study participants were assigned to diagnostic group categories during ADPR/ADRC consensus committee meetings consisting of a geriatrician, neurologists, neuropsychologists, psychometrist, and nurses who had seen the patient. The same consensus committee members assigned diagnostic group category to patients at both the first and second clinical followup point. Categorization into diagnostic groups represented a clinical judgment which was based on the combined results of medical history, clinical exam, and psychometrics. Criteria for the diagnosis of cognitively normal controls were: 1) no active neurologic or psychiatric disorders, 2) while some subjects may have had ongoing medical problems, the illnesses or their

treatments did not interfere with cognitive function, 3) a normal neurological exam, and 4) no psychoactive medications, 5) were independently functioning community dwellers. The diagnosis of probable AD was made according to the Diagnostic and Statistical Manual for Mental Disorders, III Edition–Revised (DSM-III-R) Criteria for dementia, and National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association Criteria (NINCDS/ADRDA) for AD(8,9). The severity of dementia was graded by the clinical dementia rating (CDR) score(10). Criteria for the diagnosis of MCI were: 1) memory complaint documented by the patient and collateral source; 2) normal general cognition, 3) normal activities of daily living; 4) not demented (DSM-III-R) (8); 5) CDR score of 0.5 (1,2,11). Fixed cutoff scores on specific psychometric tests of general cognitive performance and memory were not employed. The diagnosis of MCI was a clinical categorization of individuals who displayed an isolated memory impairment with preservation of other cognitive functions.

In addition to the initial diagnostic group assignment each control and MCI subject was further classified as either stable or a decliner. Subjects were designated as stable if their clinical classification assigned by the ADPR/ADRC consensus committee did not change, i.e. controls remained controls, and MCIs remained MCIs. Subjects were designated as decliners if their clinical classification changed, i.e. control subjects evolved to MCI or AD or MCI subjects progressed to AD. Apolipoprotein E (APOE) genotyping was performed in all subjects (12). All subjects also underwent a MRI examination of the brain performed according to a standardized protocol. The maximum interval between MRI and clinical assessments was ± 2 months in 125 subjects, ± 4 months in 3 subjects, and ± 6 months in a single subject. These MRI studies were used in the diagnostic process only to identify treatable causes of cognitive impairment. The hippocampal volume data derived from the MRI examination and APOE genotypes were not known to the ADPR/ADRC consensus committee throughout the study.

MRI Methods

All patients were imaged at 1.5T (Signa, General Electric Medical Systems, Milwaukee, WI) using a standardized imaging protocol (13). Measurements of intracranial volume were derived from a T1-weighted sagittal sequence with 5 mm contiguous sections. Volume measurements of the hippocampi were derived from a T1-weighted (3D) volumetric spoiled gradient recalled echo sequence with 124 contiguous partitions, 1.6 mm slice thickness, a 22 cm $\times$ 16.5 cm field of view, 192 views, and 45° flip angle.

All image processing steps in every patient were performed by the same research associate who was blinded to all clinical information (age, gender, and clinical status). The date of each MRI scan was also masked in the digital image file so that the hippocampal measurements were done without knowledge of the chronologic ordering of the scans in each pair. An automated image registration program was employed to co-register the 3D image dataset of the first scan to that of the second scan. The image data of both scan 1 and scan 2 were then interpolated inplane to the equivalent of a 512 $\times$ 512 matrix and magnified times 2. The voxel size of the fully processed image data was 0.316 mm³. The images of the whole brain were then subvolumed to include the temporal lobes. An intensity inhomogeneity correction algorithm developed in-house was then applied to both MRI scans. After the boundaries of the hippocampi had been delineated on each anatomic slice, the number of voxels was calculated automatically with a summing region of interest function. These were multiplied by voxel volume to give a numeric value in mm³ (14).

The borders of the right and left hippocampi were manually traced with a mouse driven cursor for each slice sequentially from posterior to anterior. Inplane hippocampal anatomic boundaries were defined to include the CA1 through CA4 sectors of the hippocampus proper, the dentate gyrus, and subiculum (15). The posterior boundary of the hippocampus was determined by the

oblique coronal anatomic section on which the crura of the fornices were identified in full profile. Thus, essentially the entire hippocampus head through tail was included in these measurements. Intracranial volume was determined by tracing the margin of the inner table of the skull on contiguous images from the sagittal sequence.

Statistical Methods

The annualized percent change in hippocampal volume was computed as the volume in mm³ of scan 2 minus that of scan 1 divided by volume on scan 1, divided by the duration (in years) between the two scans ($\times 100$). Like most patient registries, our ADPR/ADRC studies employ a rolling enrollment method. This results in a database consisting of patients with variable intervals between baseline enrollment and the most recent followup. By restricting the analysis in this study to those individuals with 3 ± 1 years of followup duration, we were able to minimize the statistical difficulties that otherwise would have been associated with comparing patients with different followup intervals. In addition, the rate of hippocampal volume change was calculated over the same period of observation covered by the two clinical assessment points, which temporally coupled change or absence of change in cognitive status with change in hippocampal volume. Comparisons were based on a two-way (baseline clinical group and stable/decliner) analysis of variance (ANOVA) on the ranked data. Statistically significant findings in the ANOVA were further explored using rank sum tests.

In order to compare the baseline hippocampal volume (i.e., hippocampal volume at the time of the initial MR scan) among groups, the hippocampal volume measurements were normalized for interindividual variation in head size, age, and gender (16). The hippocampal volumes in each individual were summed and divided by the total intracranial volume of that particular patient to control for variation in head size. We have previously determined age and gender specific normal percentiles for normalized hippocampal volume in a group of 126 cognitively normal elderly controls (17). Age and gender specific normal percentiles for each of the 129 participants in the current study were determined using this normal value database. Each percentile was then converted to a W score. The W score is the value from a standard normal distribution corresponding to the observed percentile in controls. For example, for a standard normal distribution, the 50th, 5th, and 2.5th percentiles are given by 0, -1.64, and -1.96. Thus, a patient with a hippocampal volume (after adjustment for age and gender) at the 5th percentile in the normal value database would receive a W score of -1.64. Similarly, a patient at the 50th percentile would receive a W score of 0. When this method of assigning W scores is applied to the normal elderly control database, the resulting W scores precisely follow a standard normal distribution. W scores in other study populations can then be compared directly to this standard distribution, providing a framework for comparing hippocampal volume measurements among individual subjects which have been appropriately corrected for age, gender, and head size.

Results

Characterization of Subjects

Descriptive information is found in Table 1. Over the course of the observation period 10 (17%) of the initial cohort of 58 controls declined to either the MCI or probable AD categories. Eighteen (42%) of the initial cohort of 43 MCIs declined to the AD category. The proportion of women in each clinical group was $\geq 50\%$ reflecting the over representation of women among the elderly. The proportion of individuals with APOE genotypes that elevate the risk for developing AD ($\epsilon 3/4$ or $\epsilon 4/4$) increased in the following order: control-stable < control-decliner < MCI-stable < MCI-decliner < AD. The MMSE and DRS scores at baseline declined in the following order: control-stable > control-decliner > MCI-stable > MCI-decliner > AD (18).

The Rates of Volume Change

The annualized rates of hippocampal volume loss for each of the three initial clinical groups decreased progressively in the following order: AD > MCI > C (Table 2). The differences between the control and MCI groups, and between control and AD groups were significant at $p < 0.001$. The annualized percent change in hippocampal volume in each of the five followup clinical groups is summarized in Table 3. The p-values obtained by pair-wise between group comparisons in Table 3 which were significant or nearly so ($p < 0.10$) were: control-stable vs control-decliner, $p = 0.03$; control-stable vs MCI-stable, $p = 0.02$; control-stable vs MCI-decliner, $p < 0.000$; control-stable vs AD, $p < 0.000$; MCI-stable vs MCI-decliner, $p = 0.03$; MCI-stable vs AD, $p = 0.06$. The calculated annualized percent change in hippocampal volume was ≤ 0 , indicating volume loss over time, in 128 of the 129 subjects. A positive volume change over time of +0.1% was measured in one of the stable AD patients.

Baseline Volumes

The baseline hippocampal volume in each of the three initial clinical groups decreased progressively in the following order: control > MCI > AD (Table 4). The differences among all three baseline groups were significant at $p < 0.000$. Baseline hippocampal volumes for each of the five followup clinical groups appear in Table 5 where the values are expressed both in terms of the W score as well as corresponding calculated percentile with respect to normal controls after adjustment for age, sex, and head size. The p values obtained by pairwise between-group comparisons in Table 5 which were significant or nearly so ($p < 0.10$) were: control-stable vs control-decliner, $p = 0.09$; control-stable vs MCI-stable, $p = 0.01$; control-stable vs MCI-decliner, $p < 0.000$; control-stable vs AD, $p < 0.000$; control-decliner vs AD, $p = 0.01$; MCI-stable vs MCI-decliner, $p = 0.05$; MCI-stable vs AD, $p < 0.000$.

Discussion

Both MRI and CT have been used to assess rates of global hemispheric atrophy or ventricular enlargement in AD (19–24). The goals of the study were to measure the annualized rates of hippocampal volume change in different clinical groups who lie along the cognitive continuum, normal to MCI to AD, and to test the hypothesis that these rates differed as a function of initial and followup group membership. Dividing the cognitive continuum into control, MCI, and AD groups can be construed as artificial, but is commonly done for descriptive clinical purposes, for example, dividing the continuous measure of blood pressure into a normal and abnormal range. As no single test is accepted for defining discrete ranges within the cognitive continuum, we chose to use the designations of control, MCI, and AD which are ultimately clinical judgments that are derived from a number of different factors. We also acknowledge that dichotomization of the control and MCI groups into those who remained stable vs decliners is a crude way to define change in cognition because the change in cognition over time occurs as a continuous rather than a step-wise function. A patient may well have experienced a mild cognitive decline over time yet still be classified as stable if the magnitude of the decline was not sufficient to "move" him/her to a lower functioning cognitive group. However, the design of this study lent itself to reporting results in a dichotomous fashion because some patients did and some did not change group designation over the period of observation. This also corresponds to useful clinical distinctions.

While the rates of hippocampal atrophy we report were by default a linear fit to two time points, we do not mean to imply that the rates of change in vivo are necessarily linear. MRI studies were performed at two points in time in each subject, multiple MRI exams over time in each subject would be necessary to determine whether rates of atrophy are linear or non-linear. It is also possible that different non-linear functions will best fit the data in different clinical groups.

To be included in the analysis, subjects had to have two relatively artifact free MRI studies separated by 2–4 years. This requirement would exclude patients who were unable to co-operate for a followup MRI due to rapidly progressive dementia. The reported rates of atrophy in the decliner groups may therefore be underestimated, because the largest volume loss over time should occur in patients who were the most rapid clinical decliners.

To our knowledge this is the first study which describes the rates of hippocampal atrophy in MCI patients. Our data indicate that the rates of hippocampal atrophy in MCI patients are heterogeneous. Those who declined clinically had greater rates of atrophy than those who did not. With the recent recognition of MCI as a clinically important group, controversy has arisen whether every individual who meets criteria for MCI will eventually progress to AD. Is MCI simply early AD or will some MCIs remain stable indefinitely albeit functioning at a lower level than control age mates? Our data address this question. The rate of hippocampal atrophy of cognitively stable MCIs was on average significantly greater than that of stable controls and comparable to control decliners. This observation supports the idea that some proportion of MCIs who on clinical grounds appear cognitively stable over a 3 ± 1 year period are actually undergoing anatomic changes that differ significantly from stable controls, and therefore are progressing toward AD. However, our data also demonstrate that the rate of atrophy in MCI decliners was significantly greater than that in stable MCIs and in this respect support the notion that some patients who meet the criteria for MCI may remain relatively stable.

On the surface the term control-decliner is a misnomer. Certainly individuals who began the study as controls but declined to MCI or AD were actually in a presymptomatic phase of AD at baseline. However, they were functioning at a level which placed them into our operationally defined control category. AD pathology then progressed between baseline and followup to such an extent that cognitive impairment became clinically apparent. Prior studies on rates of hippocampal atrophy have not distinguished stable controls from control decliners. The rate which we calculated in this study for stable controls ($-1.73\%/year$) is very close to the $-1.55\%/year$ which we calculated in a previous study (6), and is comparable to that described for older controls (-2.09%) by another group (25). While subjects were excluded from our study if they had experienced a stroke either before or during the observation period, none of the subjects, patients or controls, were excluded by the presence of vascular risk factors such as hypertension, cardiovascular disease, or diabetes (26). The prevalence of these conditions therefore should be present in our subjects roughly in the same proportion as in the general elderly population. The rate of hippocampal atrophy calculated for our group of stable controls should be representative of cognitively stable elderly individuals in the general population.

The annualized rate of hippocampal volume loss in probable AD patients in a prior longitudinal study of ours was 3.98% (6). This is close to the rate of $3.5\%/yr$ observed in the current study. This rate was also within the range described in another study (27) using MRI volumetrics, but less than described by a different group (28) who measured the change in thickness of the medial temporal lobe on CT. Over the course of longitudinal clinical observation 17 members of the AD group declined to a lower functioning level as defined by an increase in CDR score, and the remaining 11 retained their baseline CDR score. This indicates the clinical heterogeneity of disease progression within this group. We elected to not analyze rates of atrophy separately for AD-decliners vs "AD-stable". AD is by definition a progressive disorder and so designating a group as "stable" ADs seemed counterintuitive.

We have previously shown however, that baseline hippocampal volume can provide predictive information about which MCIs will decline to AD vs which will remain stable (29). In the current study as well, baseline hippocampal volumes of MCI decliners were significantly more atrophic than those of stable MCIs. A trend was present indicating that baseline hippocampal volumes were more atrophic in control-decliners than in stable controls ($p = 0.09$). The number

of controls who converted was fairly small (n=10). We believe that with a larger sample size, the difference in baseline hippocampal volume between stable vs declining controls and may reach statistical significance. Other groups have also shown that assessments of hippocampal atrophy can provide predictive information in patients who are at elevated risk for AD(27, 30). Whether the rate of hippocampal atrophy can add to this prediction is unclear and is not formally addressed in this study. However, the fact that the rates of hippocampal atrophy were significantly different between stable controls vs control decliners and between stable MCI vs MCI decliners, shows promise that the rate of hippocampal atrophy may add additional predictive power to baseline hippocampal volume in assessing the risk of converting to AD for individual patients. This remains to be determined however, and diagnostic utility in predicting future development of AD in individuals will likely be limited by inter-group overlap.

In any individual patient the pathologic progression leading to AD may extend over decades. Sampling clinically defined groups of patients who span the cognitive continuum with serial MRI studies permits ascertainment of rates of anatomic change which are characteristic of the disease at various points in its decades-long time course. This is a potentially useful tool with which to characterize one feature of the natural history of the disease—brain atrophy.

An important consideration in assessing the utility of any biomarker is its reproducibility. In the current context the parameter of interest is the reproducibility of serial hippocampal volume measurements. In a prior study of serial hippocampal volume measurements in normal young adults we demonstrated a median coefficient of variation of 0.28% (0.02% – 0.70%) (6). Theoretically the measured change in hippocampal volume in every elderly individual should be ≤ 0 , indicating either no change or volume loss over time. In the current study, measurements in 128 out of 129 patients met this criteria. A positive change over time, an increase in volume of 0.1%, was measured in one of the patients. We attribute this to measurement error.

The data presented demonstrate a correlation between the rate of change in hippocampal volume and change in cognitive status. Serial measurements of hippocampal volume may therefore be a useful adjunctive tool to monitor the efficacy of therapeutic trials in groups of patients. If a therapeutic agent slows or arrests the anatomic progression of AD pathology, this should be detectable as a decrease in the rate of atrophy in a treated vs a placebo group. Our data also indicate that the distinction between stable vs a declining members of a group should be detectable both in early symptomatic patient groups (i.e., MCI) and in presymptomatic subjects (i.e., controls).

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Table 1

Descriptive Information

	Female Gender	ApoE4 ¹	Age at 1 st MRI	Education ²	MMSE ³	DRS ⁴	Duration between baseline and followup MRI in years
Control-Stable (N=48)	33 (69%)	5 (10%)	80.4 ± 6.4 (62, 97)	13.9 ± 2.7 (8, 20)	28 ± 1.6 (23, 30)	136 ± 5.2 (122, 144)	3.0 ± 0.5 (2.0, 3.9)
Control-Decliner (N = 10)	5 (50%)	2 (20%)	82.3 ± 5.8 (76, 95)	11.4 ± 3.2 (8, 16)	28 ± 1.7 (25, 30)	133 ± 5.4 (126, 142)	3.3 ± 0.4 (2.7, 4.0)
MCI-Stable (N = 25)	14 (56%)	7 (28%)	77.9 ± 7.6 (60, 92)	14.0 ± 3.1 (8, 20)	27 ± 1.9 (23, 30)	129 ± 5.7 (115, 140)	2.9 ± 0.5 (2.1, 4.0)
MCI-Decliner (N = 18)	9 (50%)	7 (39%)	77.3 ± 8.0 (64, 94)	13.1 ± 3.1 (7, 18)	24 ± 3.2 (18, 30)	121 ± 10.6 (101, 138)	2.9 ± 0.6 (2.1, 3.9)
AD (N = 28)	22 (79%)	13 (46%)	73.8 ± 11.3 (51, 93)	12.7 ± 2.7 (5, 18)	22 ± 4.3 (14, 29)	114 ± 14.4 (74, 136)	2.9 ± 0.5 (2.1, 3.9)

Values for continuous variables in the table are: mean ± SD (range)

¹ Proportion of individuals with APOE genotypes ε3/ε4 or ε4/ε4;

² Maximum educational attainment;

³ MMSE = Mini-Mental Stateexamination;

⁴ DRS = Dementia Rating Scale

Table 2
Percent Annual Change in Hippocampal Volume By Initial Clinical Group

Control (N = 58)	-1.9 ± 1.1 (-5.3, -0.1)
MCI (N = 43)	-3.0 ± 1.6 (-7.5, -0.1)
AD (N = 28)	-3.5 ± 1.8 (-6.9, 0.1)

Values in Table represent mean $\pm$ SD (range)

Table 3

Percent Annual Change in Hippocampal Volume by Followup Clinical Group

Control-Stable (N = 48)	-1.7 ± 0.9 (-3.8, -0.1)
Control-Decliner (N = 10)	-2.8 ± 1.7 (-5.3, -0.1)
MCI-Stable(N = 25)	-2.5 ± 1.5 (-4.8, -0.1)
MCI-Decliner (N = 18)	-3.7 ± 1.5 (-7.5, -1.7)
AD (n=28)	-3.5 ± 1.8 (-6.9, 0.1)

Values in table represent mean ± SD (range)

Table 4
Baseline Hippocampal Volume by Initial Clinical Group

Group	W Score ¹	Percentile ²
Control (N = 58)	-0.2 ± 1.2 (-2.5, 2.9)	41
MCI (N = 43)	-1.2 ± 1.3 (-4.6, 1.3)	11
AD (N = 28)	-2.1 ± 1.2 (-4.0, 0.9)	2

¹ mean ± SD (range)

² Median normal percentile value

Table 5
Baseline Hippocampal Volume By Followup Clinical Group

Group	W Score	Percentile
Control-Stable (N = 48)	-0.1 ± 1.2 (-2.5, 2.9)	47
Control-Decliner (N = 10)	-1.0 ± 1.3 (-2.5, 0.8)	16
MCI-Stable (N = 25)	-0.9 ± 1.4 (-4.0, 1.3)	18
MCI-Decliner (N = 18)	-1.7 ± 1.3 (-4.6, 0.9)	5
AD (N=28)	-2.1 ± 1.2 (-4.0, 0.9)	2

¹ Mean $\pm$ SD (range)

² Median normal percentile value (range)