Volume 24, No 3 | International Journal of Radiation Research, July 2026

MRI-based evaluation of brain volume changes in patients with Alzheimer's disease over time

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► ***Original article***

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Received: December 2025
Final revised: April 2026
Accepted: May 2026

Int. J. Radiat. Res., July 2026; 24(3): 741-748

DOI: 10.61186/ijrr.24.3.22

Keywords: *Alzheimer disease, magnetic resonance imaging, brain atrophy, hippocampus, entorhinal cortex, ventricular enlargement.*

ABSTRACT

Background: Magnetic resonance imaging (MRI) may reveal quantifiable and structural changes to the brain as a result of Alzheimer's disease (AD), an irreversible neurodegenerative disease. Longitudinal evaluation of alterations in brain volumes presents essential information on disease development and evaluation of therapeutic response. ***Materials and Methods:*** The study was a prospective longitudinal cohort study that included 156 subjects (78 AD patients and 78 age-matched healthy controls). The baseline, 12 months, and 24 months high-resolution 3T MRI scan were taken. FreeSurfer software was used to perform automated volumetric analysis in order to measure total brain volume (TBV), hippocampal volume (HV), entorhinal cortex volume (ECV) and ventricular volume (VV). ***Results:*** AD participants showed a substantially higher rate of total brain volume loss (2.18 + 0.67/ vs. 0.52 + 0.24) and hippocampal atrophy (4.82 + 1.34/ vs. 0.89 + 0.41) each year than the controls. The AD patients experienced significant acceleration of enlargement of the ventricles (8.94 ± 2.87% vs. 2.14 ± 0.92%, $p<0.001$). The greatest discriminative ability between groups was observed with the entorhinal cortex volume (AUC = 0.94). There was great predictive value of baseline hippocampal volume with regard to the cognitive decline trajectory ($r = -0.72$, $p<0.001$). ***Conclusion:*** The volumetric MRI study demonstrates that in Alzheimer disease, there are accelerated and regional atrophy patterns of the brain. These results endorse the relevance of longitudinal structural MRI as a potent biomarker of disease progression and possible therapeutic effect of new clinical trials.

INTRODUCTION

"Alzheimer disease (AD) is the most common neurodegenerative condition in the world, with the disease prevalence of between 60-80 percent of all cases of dementia and individuals with the disease are above 55 million worldwide [1]. The condition is marked by cognitive decline, memory loss and functional decline that severely affect the quality of life and cause huge burden on both the health care systems and the carers [2]. The global population is aging, and it has been estimated that the incidence of AD will increase threefold by the year 2050 hence the necessity to develop better diagnostic and monitoring instruments [3].

The neuropathological characteristics of AD are extracellular amyloid-bet plaques; intracellular neurofibrillary tangles made up of hyperphosphorylated tau protein and progressive neuronal degeneration with resulting atrophy of the brain on a macroscopic scale [4]. Such pathological alterations can be initiated many years to decades prior to the development of clinical symptoms, and in that case, structural changes take place in the brain and ultimately lead to cognitive impairment [5]. It is important to learn the temporal dynamics of these structural changes to intervene in diseases early and manage them.

Magnetic resonance imaging (MRI) has become an essential procedure in the assessment of neurodegenerative disorders by providing non-invasive, repeatable and quantitative measures of brain structure [6]. Structural MRI allows the determination of regional and global brain volumes with great accuracy and can be used to identify patterns of atrophy typical of AD. The first and most significant volumetric changes in AD refer to the structures of the medial temporal lobe, in particular, hippocampus and the entorhinal cortex, which indicates the local specificity of tau pathology [7].

Alzheimer World has made significant progress in the field of neuroimaging biomarkers in AD, specifically with the Alzheimer Disease Neuroimaging Initiative (ADNI) which has produced substantial amounts of information on the subject of neuroimaging biomarkers and their application in AD research [8]. Cross-sectional studies have also shown that hippocampal volumes in AD patients are lower than those of the healthy controls, and the sensitivity and specificity of this condition have been over 80 percent in separating these two groups [9]. But volumetric MRI is not limited to diagnosis classification but can be used in treatment to classify and also prognose as well as observe disease progression with time.

Longitudinal MRI imaging has found that atrophy

of the brain rather than absolute brain volume at one time point shows a higher sensitivity as a disease activity [10]. Hippocampal atrophy rates among AD patients have been reported to be between 3.5 and 5.9 percent at the age of one year, relative to 0.5 and 1.5 percent in the cognitively normal elderly persons [11]. Such increased rates of atrophy are linked to cognitive impairment and can be used as predictors of mild cognitive impairment to dementia [12].

New technological advances have been applied in automated volumetric analysis in order to increase reliability and reproducibility of the brain volume measurements [13]. The software packages like FreeSurfer allows standard cortical and subcortical segmentation pipelines that can be used to measure the same variables at multiple time points and across study locations [14]. Such methodological advances have enabled the incorporation of volumetric MRI into the clinical trials as outcome measures and also provided support on the construction of normative databases in the assessment of individual patients.

Even though significant advances have been made, there are still various gaps in the longitudinal brain volume changes in AD. To start with, the comparative sensitivity of various brain regions as markers of progression of the disease in the disease course needs to be better clarified. Second, the connection between regional atrophy patterns and individual cognitive domains should be investigated further. Third, the possibility of a demographic and clinical effect on the rate of atrophy requires a thorough study in various populations [15].

Moreover, although the literature on brain volume studies has been done in many studies in the Western populations, there is paucity in the literature on various ethnic and geographic groups [16]. Knowledge of the difference in atrophy patterns and rates among people is needed to determine biomarker thresholds with universal applicability and interpolate outcomes in international clinical practice.

The current research was a large-scale attempt to assess the pattern and rate of changes in brain volume of patients with Alzheimer disease and of cognitively normal control groups over 24 months using high-resolution volumetric MRI. In particular, we aimed to: (1) measure the annual rates of atrophy in major brain structures such as total brain and hippocampus volume, entorhinal cortex and ventricles volume; (2) find out discriminative capacity of baseline volumes and atrophy rates in differentiating between AD and healthy patients; and (3) establish the relationship between structural brain change and the trajectory of cognitive decline. Our hypothesis was that the AD patients would exhibit faster rates of atrophy especially on the medial temporal lobe structures, and that such change would be associated with the worsening of cognitive abilities over time.

This study provides a prospective longitudinal volumetric MRI assessment of Alzheimer disease patients over a 24-month follow-up period using a standardized 3T MRI protocol and automated FreeSurfer longitudinal processing. Unlike many cross-sectional volumetric studies, this work quantifies annual percentage atrophy rates across multiple brain regions and evaluates their diagnostic performance using ROC analysis. Additionally, it establishes strong predictive correlations between baseline hippocampal volume, longitudinal hippocampal atrophy rate, and cognitive decline trajectory, highlighting the prognostic value of serial volumetric MRI biomarkers in clinical monitoring and therapeutic trials.

MATERIALS AND METHODS

Study design and participants

The research spanned 24 months and used a prospective longitudinal cohort strategy. The study included 156 people: 78 with a confirmed diagnosis of Alzheimer's disease (AD) and 78 healthy controls who were age-and sex-matched and had normal cognitive function. Neurology and memory clinics that treat outpatients were used for recruitment. Baseline assessments were conducted at the time of enrolment, followed by scheduled evaluations at 12 months and 24 months.

Sample size estimation was performed a priori using previously reported hippocampal atrophy rates in AD. Assuming an effect size of 0.8, alpha error probability of 0.05, and statistical power of 0.90, the minimum required sample size was calculated as 68 subjects per group. To account for possible attrition during follow-up, 78 participants were enrolled in each group.

Inclusion and exclusion criteria

To be included in the AD group, patients had to meet the following criteria: they had to be 55 to 85 years old, their MMSE scores had to be between 15 and 26, and their CDR scores had to be between 0.5 and 2.0. These criteria were based on the guidelines set by the National Institute on Aging-Alzheimer's Association (NIA-AA). Patients had to be on stable doses of medicine for Alzheimer's disease, including memantine or cholinesterase inhibitors, for a minimum of three months before they could join. A reliable caregiver or study partner was required to provide collateral clinical history and assist with follow-up assessments.

Control participants were included if they had no subjective cognitive complaints, normal cognitive screening performance (MMSE ≥ 28), a CDR score of 0, no first-degree family history of dementia, and were matched to the AD group for age and sex.

Participants from both groups were excluded if they had any neurological disorders other than AD, including stroke, brain tumours, epilepsy, or multiple

sclerosis. Substance misuse or dependency, serious mental disease (e.g., schizophrenia or severe depressive disorder), and medical conditions that prevent magnetic resonance imaging (MRI), such as pacemakers, were also considered exclusion criteria, metallic implants, or claustrophobia, and significant systemic illnesses that could interfere with participation or survival during follow-up".

Clinical and cognitive assessment

All participants underwent standardized clinical and neuropsychological assessments at baseline, 12 months, and 24 months. Evaluations were conducted by trained neuropsychologists who were blinded to MRI volumetric findings. To measure global cognitive function, the MMSE and the Montreal Cognitive Assessment (MoCA) were administered. The CDR scale and CDR Sum of Boxes (CDR-SB) were used to assess the severity of dementia. The cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog 13) was used to further evaluate cognitive function. The Digit Span Forward and Backward tests and the Rey Auditory Verbal Learning Test (RAVLT) were used to evaluate focus and memory. The Trail Making Test, Parts A and B, were used to evaluate cognitive abilities and processing speed. while language function was evaluated using the Boston Naming Test.

Functional status was assessed using the Functional Activities Questionnaire (FAQ) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale.

MRI acquisition protocol

An MRI scanner with 64 channels was used for all scans; the scanner in question was a 3.0 Tesla Siemens Magnetom Prisma from Siemens Healthineers in Erlangen, Germany. Imaging was performed at baseline, 12 months, and 24 months using the same scanner and acquisition parameters to maintain consistency across follow-up time points.

The MRI protocol included a high-resolution three -dimensional T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with repetition time (TR) of 2300 ms, echo time (TE) of 2.98 ms, inversion time (TI) of 900 ms, flip angle of 9°, field of view (FOV) of 256 × 256 mm^2, matrix size of 256 × 256, slice thickness of 1.0 mm isotropic, and 176 sagittal slices. Additionally, a three-dimensional T2-weighted FLAIR sequence was obtained with TR of 5000 ms, TE of 388 ms, TI of 1800 ms, and isotropic slice thickness of 1.0 mm. A T2-weighted turbo spin echo sequence was also acquired to assess vascular lesions and structural abnormalities.

All images underwent quality control by radiologists, including inspection for motion artifacts, signal distortion, and incomplete brain coverage. Images with unacceptable quality were excluded from analysis.

Image processing and volumetric analysis

Volumetric MRI analysis was performed using FreeSurfer software (FreeSurfer version 7.2, Massachusetts General Hospital, Boston, MA, USA). The standard automated cortical and subcortical segmentation pipeline was applied. To improve sensitivity for longitudinal detection of subtle volume changes, the FreeSurfer longitudinal processing stream was utilized, which generates an unbiased within-subject template for each participant.

Segmentation of subcortical gray and white matter regions, intensity normalization, motion correction, skull stripping, and Talairach transformation were all steps in the processing pipeline, cortical surface reconstruction, topology correction, and automated parcellation of cortical regions.

Complete brain volume (TBV), total gray matter volume, total white matter volume, hippocampus volume (HV), entorhinal cortex volume (ECV), parahippocampal gyrus volume, temporal lobe gray matter volume, and lateral ventricular volume (VV) were the main volumetric results that were retrieved. In order to standardize, the total intracranial volume (TIV) was determined. In order to account for variations in head size across individuals, all regional volumes were adjusted to TIV.

Annual percentage volume change was calculated using the formula: [(Follow-up volume − Baseline volume) / Baseline volume × 100] / years.

The study protocol was reviewed and approved by the Institutional Research Ethics Committee, College of Medicine, Qassim University, Buraydah, Saudi Arabia (Approval No.: QU-COM-REC-2024-017, Date of Approval: 12 January 2024). Prior to registration, all participants or their legally authorized representatives were asked to provide written informed consent. The Declaration of Helsinki was followed throughout the course of the research.

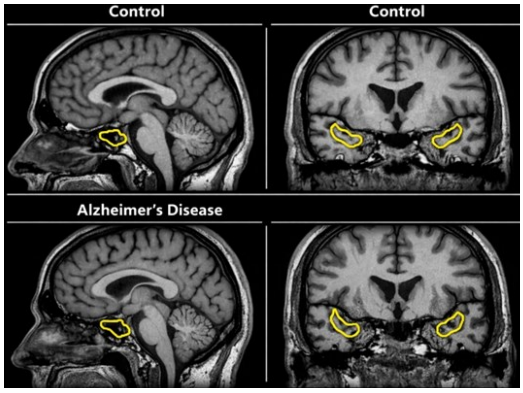

Figure 1. Representative T1-weighted 3T MRI images demonstrating hippocampal atrophy in Alzheimer disease (AD) patient compared to age-matched control. Sagittal and coronal T1-weighted images demonstrate reduced hippocampal volume and medial temporal lobe atrophy in AD. Images were acquired using Siemens Magnetom Prisma 3T MRI (Germany).

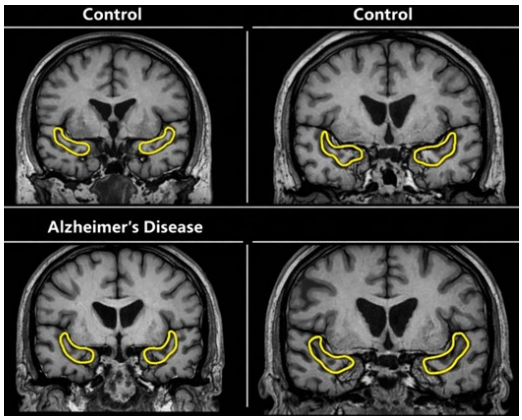

Figure 2. Representative MRI images showing ventricular enlargement in Alzheimer disease (AD) compared to healthy control. Axial and coronal T1-weighted MRI images demonstrate prominent lateral ventricular enlargement in AD patients consistent with progressive parenchymal volume loss.

All MRI scans were performed using a 3.0 Tesla Siemens Magnetom Prisma scanner (Siemens Healthineers, Erlangen, Germany). Automated volumetric processing was performed using FreeSurfer software version 7.2 (Massachusetts General Hospital, Boston, MA, USA). Statistical analysis was conducted using IBM SPSS Statistics version 28.0 (IBM Corporation, Armonk, NY, USA) and R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Statistical analysis

Research was conducted using R statistical software version 4.2.1 and IBM SPSS Statistics version 28.0, both developed by IBM Corporation and located in Armonk, NY, USA. For continuous data, the standard deviation (SD) was used to indicate the mean, and for categorical variables, the frequency and percentage were used. In order to determine whether the data followed a normal distribution, we used the Shapiro-Wilk test and graphical tools like histograms and Q-Q plots. For continuous variables, we used independent samples t-tests, and for categorical variables, we used chi-square tests, to compare the groups' baseline demographic and clinical features. By using analysis of covariance (ANCOVA) and controlling for age, sex, and education level, we compared group measurements of volumetric MRI at each time point. We used linear mixed-effects models with random intercepts and slopes to examine longitudinal changes. This allowed us to account for repeated measurements and intra-subject variability. Group, time, and the interaction between groups and time were all considered fixed effects, with age, sex, and education serving as variables. To measure the efficacy of volumetric biomarkers as diagnostic tools, researchers used receiver operating characteristic (ROC) curve analysis. Positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, appropriate cutoff values, and area under the curve (AUC) were computed. Using Pearson correlation coefficients, we assessed the associations between cognitive outcomes and volumetric MRI measurements. To find factors that might independently predict cognitive deterioration, researchers used several linear regression models. Statistical significance was defined as $p<0.05$ (two-tailed), and false discovery rate (FDR) correction was applied for multiple comparisons.

RESULTS

Participant characteristics

Among 156 participants who were assigned to the study, 148 had gone through the 24 months follow-up (retention rate: 94.9%). Eight of the participants were not included in the final analysis because of their death (n = 3), a lack of consent (n = 2), and low quality of MRI data (n = 3). The analysis was finally done on 74 AD patients and 74 controls.

Table 1 displays baseline demographic and clinical characteristics. The ages in the groups were also very similar (AD: 72.4 ± 6.8 years vs. controls: 71.6 ± 7.2 years, p = 0.482) as well as the sex distribution (AD: 54.1% female vs. controls: 51.4% female, p = 0.742). The level of education was also a bit low in the AD group (12.8 +/-3.4 years vs. 14.1 +/-3.2 years, p = 0.018). Predictably, the baseline cognitive scores of AD patients showed a great deal (all $p<0.001$) lower than those of controls. There were no statistically significant variations in the age and sex distribution between the AD and control groups based on baseline demographic parameters ($p>0.05$). However, education level was significantly lower in the AD group (12.8 ± 3.4 years) compared to controls (14.1 ± 3.2 years) (p = 0.018). As expected, baseline cognitive scores including MMSE, MoCA, CDR-SB, and ADAS-Cog 13 were significantly impaired in the AD group compared to controls (all $p<0.001$), confirming the clinical validity of group classification.

Table 1. Baseline demographic and clinical characteristics of study participants.

Variable	AD Group (n = 74)	Control Group (n = 74)	p-value
Age (years)	72.4 ± 6.8	71.6 ± 7.2	0.482
Sex (female, %)	40 (54.1%)	38 (51.4%)	0.742
Education (years)	12.8 ± 3.4	14.1 ± 3.2	0.018*
APOE ε4 carriers (%)	48 (64.9%)	18 (24.3%)	<0.001***
Disease duration (years)	3.2 ± 1.8	-	-
MMSE score	21.4 ± 3.6	29.2 ± 0.8	<0.001***
MoCA score	17.2 ± 4.2	27.8 ± 1.4	<0.001***
CDR-SB	4.8 ± 2.1	0.04 ± 0.12	<0.001***
ADAS-Cog 13	28.6 ± 8.4	7.2 ± 3.1	<0.001***
FAQ score	12.4 ± 6.8	0.3 ± 0.6	<0.001***
Cholinesterase inhibitor use (%)	62 (83.8%)	0 (0%)	<0.001***
Memantine use (%)	34 (45.9%)	0 (0%)	<0.001***

Data are presented as mean ± SD or n (%). AD: Alzheimer Disease; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; CDR-SB: Clinical Dementia Rating-Sum of Boxes; ADAS-Cog: Alzheimer Disease Assessment Scale-Cognitive Subscale; FAQ: Functional Activities Questionnaire.

Baseline brain volumes

All of the brain areas examined indicated statistically significant group differences according to the baseline volumetric values (table 2). Brain volumes in both Alzheimer's disease patients and healthy controls (1082.4 ± 98.6 cm^3 vs. 1198.7 cm^3 ± 87.4 cm^3, p=0.001) were found to be dramatically smaller (9.7%) in the former. The most significant of these differences were found in the structures of the medial temporal lobes with the reduction of the hippocampal volume by 24.8 (5.42 + 0.84 cm^3 vs. 7.21 + 0.72 cm^3, p=0.001) and entorhinal cortex volume by 28.4 (2.18 + 0.42 cm^3 vs. 3.04 + 0.38 cm^3, p=0.001.

On the other hand, patients with AD had had much larger lateral ventricular volume (48.6 ± 18.4 cm^3 vs. 28.4 ± 12.6 cm^3, p<0.001), which was a result of compensatory enlargement by parenchymal loss. All the volumetric variation was significant even after age, sex, and education (all p<0.001). At baseline, AD patients exhibited significantly reduced total brain volume (1082.4 ± 98.6 cm^3) compared to controls (1198.7 ± 87.4 cm^3) (p<0.001). The most pronounced reductions were observed in medial temporal lobe structures, where hippocampal volume and entorhinal cortex volume were reduced by approximately 24.8% and 28.4%, respectively (both p<0.001). Conversely, lateral ventricular volume was significantly enlarged in the AD group compared to controls (p<0.001), consistent with compensatory ventricular expansion secondary to parenchymal atrophy. Longitudinally, annual atrophy rates were significantly accelerated in AD patients across all regions (all p<0.001), with entorhinal cortex showing the highest annual decline (5.24 ± 1.56%).

Table 2. Baseline brain volumes and annual percentage volume changes over 24 months.

Brain Region	AD Baseline (cm^3)	Control Baseline (cm^3)	p-value	AD Annual Change (%)	Control Annual Change (%)	p-value
Total Brain Volume	1082.4 ± 98.6	1198.7 ± 87.4	<0.001***	-2.18 ± 0.67	-0.52 ± 0.24	<0.001***
Total Gray Matter	584.2 ± 56.8	658.4 ± 48.2	<0.001***	-2.42 ± 0.78	-0.61 ± 0.28	<0.001***
Total White Matter	448.6 ± 52.4	498.2 ± 46.8	<0.001***	-1.86 ± 0.54	-0.42 ± 0.22	<0.001***
Hippocampus (bilateral)	5.42 ± 0.84	7.21 ± 0.72	<0.001***	-4.82 ± 1.34	-0.89 ± 0.41	<0.001***
Entorhinal Cortex	2.18 ± 0.42	3.04 ± 0.38	<0.001***	-5.24 ± 1.56	-0.94 ± 0.48	<0.001***
Para hippocampal Gyrus	3.86 ± 0.58	4.72 ± 0.52	<0.001***	-3.68 ± 1.12	-0.72 ± 0.36	<0.001***
Temporal Lobe (GM)	98.4 ± 12.6	118.6 ± 10.8	<0.001***	-3.24 ± 0.92	-0.68 ± 0.32	<0.001***
Lateral Ventricles	48.6 ± 18.4	28.4 ± 12.6	<0.001***	+8.94 ± 2.87	+2.14 ± 0.92	<0.001***
Frontal Lobe (GM)	142.8 ± 16.4	162.4 ± 14.2	<0.001***	-1.94 ± 0.62	-0.48 ± 0.24	<0.001***
Parietal Lobe (GM)	86.2 ± 10.8	98.4 ± 9.6	<0.001***	-2.12 ± 0.72	-0.52 ± 0.26	<0.001***

Longitudinal volume changes

According to linear mixed-effects models, there were notable group × time interactions for all volumetric measurements, suggesting that AD patients and controls changed at different rates (all p<0.001). AD patients demonstrated a mean annual total brain volume loss of 2.18 ± 0.67%, compared to 0.52 ± 0.24% in controls, representing a 4.2-fold acceleration in atrophy rate.

The medial temporal lobe structures exhibited the most pronounced differential atrophy. Hippocampal volume decreased at an annual rate of 4.82 ± 1.34% in AD patients versus 0.89 ± 0.41% in controls (5.4-fold acceleration). Entorhinal cortex demonstrated the highest atrophy rate among all measured regions in AD patients (5.24 ± 1.56% annually), with a 5.6-fold acceleration compared to controls (0.94 ± 0.48% annually).

Ventricular enlargement was markedly accelerated in AD patients, with an annual expansion rate of 8.94 ± 2.87% compared to 2.14 ± 0.92% in controls (p<0.001). This 4.2-fold difference in ventricular expansion rate reflects the progressive parenchymal loss characteristic of AD.

Diagnostic performance of volumetric measures

The diagnostic performance of volumetric measurements in differentiating AD patients from controls was shown to be good in the ROC curve study (Table 3). Baseline entorhinal cortex volume showed the highest discriminative capacity (AUC = 0.94, 95% CI: 0.90-0.97), followed by hippocampal volume (AUC = 0.92, 95% CI: 0.88-0.96) and total brain volume (AUC = 0.86, 95% CI: 0.80-0.91).

"Annual hippocampal atrophy rate demonstrated superior discriminative performance compared to baseline volumes (AUC = 0.96, 95% CI: 0.93-0.99), with sensitivity of 91.9% and specificity of 93.2% at the optimal cutoff of 2.4% annual volume loss. The most accurate diagnosis was obtained by combining the baseline hippocampus volume with the yearly atrophy rate (AUC = 0.98, 95% CI: 0.96-1.00). ROC curve analysis demonstrated excellent diagnostic accuracy of volumetric biomarkers. Baseline entorhinal cortex volume showed the highest discriminative performance (AUC = 0.94), followed by hippocampal volume (AUC = 0.92). Longitudinal hippocampal atrophy rate demonstrated superior diagnostic utility compared to baseline volumes (AUC = 0.96), achieving sensitivity of 91.9% and specificity of 93.2% at an optimal cutoff of 2.42% annual decline. The combined model incorporating baseline hippocampal volume and annual hippocampal atrophy rate provided near-optimal discrimination between AD and controls (AUC = 0.98).

Table 3. Diagnostic performance of baseline volumes and annual atrophy rates for differentiating Alzheimer disease and controls.

Volumetric Measure	AUC (95% CI)	Optimal Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Baseline Volumes						
Total Brain Volume	0.86 (0.80-0.91)	1142 cm^3	79.7	78.4	78.9	79.2
Hippocampal Volume	0.92 (0.88-0.96)	6.24 cm^3	86.5	85.1	85.3	86.3
Entorhinal Cortex	0.94 (0.90-0.97)	2.58 cm^3	89.2	87.8	88.0	89.0
Lateral Ventricles	0.82 (0.76-0.88)	36.8 cm^3	75.7	77.0	76.7	76.0
Temporal Lobe (GM)	0.88 (0.82-0.93)	108.2 cm^3	82.4	81.1	81.3	82.2
Annual Atrophy Rates						
Total Brain Volume	0.94 (0.90-0.97)	1.28%	87.8	89.2	89.0	88.0
Hippocampal Volume	0.96 (0.93-0.99)	2.42%	91.9	93.2	93.2	91.9
Entorhinal Cortex	0.95 (0.91-0.98)	2.86%	89.2	91.9	91.7	89.5
Ventricular Expansion	0.92 (0.87-0.96)	4.82%	85.1	86.5	86.3	85.3
Combined Measures						
HC Volume + HC Atrophy Rate	0.98 (0.96-1.00)	-	94.6	95.9	95.9	94.7
All Temporal Volumes	0.97 (0.94-0.99)	-	93.2	94.6	94.5	93.3

AUC: Area Under the Curve; CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value; GM: Gray Matter; HC: Hippocampal.

Correlations with cognitive measures

There were strong correlations between cognitive performance and baseline volumetric measures. The Hippocampal volume showed the highest correlation with the memory measures; RAVLT delayed recall ($r = 0.68$, $p<0.001$) and the ADAS-Cog memory subscale ($r = -0.64$, $p<0.001$). Total brain volume had a significant correlation with global cognitive outcomes such as MMSE ($r = 0.58$, $p<0.001$) and MoCA ($r = 0.62$, $p<0.001$).

Longitudinal comparison showed there were high results of atrophy rates with cognitive decline. Change in MMSE score ($r = -0.72$, $p<0.001$), change in CDR-SB ($r = 0.68$, $p<0.001$) and change in ADAS-Cog 13 were significantly correlated with annual hippocampal atrophy rate ($r = 0.74$, $p<0.001$). Independent predictors of the course of cognitive deterioration were the baseline hippocampus volume, as shown by the multiple regression analysis (-0.38, $p<0.001$) and the annual rate of hippocampal atrophy (-0.42, $p<0.001$) which form 54% of the variance in MMSE change ($R 2 = 0.54$, $p<0.001$).

Subgroup analyses

Subgroup analyses based on disease severity revealed that patients with mild AD (CDR = 0.5-1.0, n = 42) demonstrated lower annual hippocampal atrophy rates compared to those with moderate AD (CDR = 1.5-2.0, n = 32) (4.12 ± 1.08% vs. 5.74 ± 1.42%, $p<0.001$). APOE ε4 carriers showed higher atrophy rates across all brain regions compared to non-carriers within the AD group (hippocampal atrophy: 5.28 ± 1.28% vs. 4.02 ± 1.12%, $p=0.001$).

Age was positively correlated with atrophy rates in both groups, but the age-related acceleration was more pronounced in AD patients. The atrophy rates of the male and female individuals in both groups did not vary significantly, according to the sex-stratified analyses (all $p>0.05$).

DISCUSSION

Within the context of Alzheimer disease, our current longitudinal study provides comprehensive quantitative data on the rapid and geographically varied patterns of brain shrinkage over the course of 24 months. We have established that AD patients have about 4- to 5-fold higher rates of volume loss than cognitively normal controls, and that the most striking differential atrophy was found in medial temporal lobe structures. These findings underscore the usefulness of volumetric MRI as a biomarker that is sensitive to protect the staging of disease progression and that have significant ramifications on clinical trials and patient care.

The rate of hippocampal atrophy of 4.82/year in our sample of AD reflects well the literature of large-scale studies. Barnes and colleagues have shown that the meta-analytic mean rate of hippocampal atrophy in patients with AD was 4.66 percent [17], and the ADNI consortium has reported rates of 3.5 to 5.5 percent depending on the severity of the disease and the method used to examine the hippocampus [18]. These benchmarks allow us to ascertain that our methodology and the overall generalizability of our findings are valid due to consistency with them.

The fact that the rate of atrophy of entorhinal cortex (5.24% per year) was significantly higher than other measured structures is due to the fact that tau pathology is preferential to this part of the brain during an early disease stage [19]. Braake distribution of neurofibrillary tangles suggests that neurofibrillary tangles engage the entorhinal cortex in the early phases of AD pathology, when there are no clinical signs of AD [20]. It is no surprise that entorhinal cortex volume demonstrated the maximum discriminative capability across groups (AUC = 0.94) since it is a prime disease marker.

The acceleration of the total brain volume loss in AD patients compared to controls is 4.2 folds which is a significant and clinically significant difference. The result has significant consequences to the design and interpretation of clinical trials in which brain volume change is becoming a secondary outcome measure [21]. This sharp distinction between groups indicates that volumetric MRI is able to identify the effects of

treatment with relatively small sample sizes, which increases the viability of therapeutic trials.

We have found that ventricular enlargement rate (8.94%/year in AD) surpassed that of parenchymal loss and this is consistent with what was found before [22]. Ventricular expansion is an indirect and a sensitive measure of tissue atrophy around and may reflect the cumulative contribution of both gray and white matter atrophy. It is a suitable biomarker in clinical practice because of its simplicity to measure the ventricular volume, as well as its relative resistance to the errors of segmentation.

Close associations between hippocampal atrophy rate and cognitive decline trajectory in this study can be used to argue that volumetric MRI measures are clinically relevant. The ability to forecast cognitive deterioration by the combination of the baseline hippocampal volume and the rate of annual atrophy was found to explain 54% suggesting the prognostic usefulness of the two measures. The previous longitudinal research studies have indicated similar relations [23], which supports the idea that clinical progression is mechanistically correlated with structural brain changes.

Clinical implications of the higher diagnostic rates of longitudinal atrophy rates than baseline volumes are significant. Although cross-sectional volumetric assessment is useful in gathering diagnostic data, longitudinal change rate reflects the activity of the disease and possibly more applicable in predicting future progression, and providing a response to treatment [24]. This fact justifies the proposal that serial MRI measurements should be introduced into a clinical practice and trial design.

In our subgroup analyses, we found significant moderating factors on the patterns of atrophy. The fact that there is higher rate of atrophy among moderate patients than the mild patients of AD implies that the disease moves faster as it advances. This nonlinearity has been reported within existing literature and it is possible that this nonlinearity mirrors the cascading nature of neurodegeneration over and above critical thresholds of pathology are reached [25]. Genetic factors also have a significant effect on the progression of the disease as demonstrated by the impact of APOE 4 carrier on the rate of atrophy.

The high diagnostic effectiveness of combining various volumetric indices (AUC = 0.98 when hippocampal volume and atrophy rate are used) indicates that multivariate methodologies have the potential to make the best use of structural MRI in clinical practice. Combination of volumetric data in other types of biomarkers, such as amyloid and tau PET imaging, cerebral spinal fluid biomarkers and cognitive testing can further improve diagnostic and prognostic accuracy [26].

This research has a number of methodological strengths that should be mentioned. The future longitudinal study that will involve uniform MRI acquisition and processing procedures increases the validity of the volumetric measures. Processing-related variability is reduced by using the longitudinal processing stream of FreeSurfer (one of which generates an unbiased within-subject template) and sensitivity is enhanced in order to detect real biological changes [27]. The detailed analysis of structure-function relationships is possible with the help of the comprehensive cognitive assessment battery.

There are a number of limitations that should be mentioned. To begin with, the sample was selected in one centre only, which may not be applicable to other populations and healthcare environments. To ensure the strength of our results, multi-centre validation studies should be used. Second, there was no pathological confirmation of AD diagnosis, which created the possibility of misclassification bias. Our stringent compliance to NIA-AA diagnostic criteria and the marked division [28] between groups in our clinical and imaging measures, however, argues that the diagnostic accuracy was high [28].

Third, the follow-up period of 24 months, though adequate to identify important differences between the groups, might not be indicative of the entire disease process. The pattern of atrophy along the course of the illness can only be described by long-term follow-up research. Fourth, the effects of concomitant medications, especially cholinesterase inhibitors and memantine, were not completely controlled despite the fact that their impact on brain atrophy is not expected to be significant in general [29].

Our results have significant clinical implications. Volumetric MRI has objective and quantitative biomarkers that can supplement clinical evaluation in the diagnosis and follow-up of AD. The evidence of sensitive response to accelerated atrophy rates is a factor that qualifies the use of serial MRI as an instrument of measuring the disease progression and possibly as the means of measuring response to disease-modifying treatments. Validated imaging biomarkers will be necessary in the selection of patients and monitoring of their treatments as new therapies focused on amyloid and tau pathology are introduced into clinical practice [30].

There are some areas that should be considered in future studies. Combination of volumetric MRI and molecular imaging modalities, as well as fluid biomarkers, can potentially allow a more accurate characterization of disease stage and prognosis. Creation of normative database in a variety of populations will enhance clinical meaning of a specific patient data. The study of previous stages of the disease, such as preclinical and prodromal AD can help see the best time points where therapeutic intervention can be applied" [31].

CONCLUSION

This prospective longitudinal volumetric MRI study demonstrated significantly accelerated global and regional brain atrophy in Alzheimer disease patients over a 24-month follow-up period compared with cognitively normal controls. Medial temporal lobe structures, particularly the hippocampus and entorhinal cortex, showed the most pronounced annual volume loss and exhibited strong associations with cognitive decline. Longitudinal hippocampal atrophy rate provided excellent diagnostic discrimination, and combined volumetric indices achieved near-optimal classification accuracy. These findings support the clinical relevance of serial structural MRI volumetry as a sensitive biomarker for monitoring Alzheimer disease progression and evaluating therapeutic response in future clinical trials.

***Acknowledgments*:** The authors would like to thank all participants and their caregivers for their cooperation and contribution to this study. The authors also acknowledge the radiology technicians and neuropsychology staff for their assistance in MRI acquisition and cognitive assessments.

***Funding*:** This research received no external funding.

***Conflict of interest*:** The authors declare no conflict of interest.

***Ethical consideration*:** The study was approved by the Institutional Research Ethics Committee, College of Medicine, Qassim University, Buraydah, Saudi Arabia (Approval No.: QU-COM-REC-2024-017; Date: 12 January 2024). Everyone who took part, or who could legally represent them, gave their written informed permission.

***Authors' contribution*:** A.A., contributed to study conception, MRI acquisition supervision, data analysis, and drafting of papers. Research strategy, statistical analysis, editing, and critical review were all areas in which B.A. had a hand. The paper was finalized with the approval of both writers.

***AI usage statement*:** No AI tool was used for data generation, statistical analysis, or alteration of scientific findings. All final content was reviewed and approved by the authors.

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