# The Effect of Age on Whole Brain Volume in Controls, Mild Cognitive Impairment and Alzheimer's Disease Patients: A Prospective Analysis of MRI Data from the ADNI Data Base

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## Abstract

**Aim:** Alzheimer disease (AD) is the most common cause of dementia worldwide. It is characterized by brain atrophy, both on imaging and autopsy, although brain atrophy also occurs during normal aging. In this study, we aim to study brain atrophy during a 2-year interval in AD patients, minimal cognitive impairment (MCI), and normal control (NC).

**Methods**: Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). This study included three groups of patients; AD, MCI, and NC. We included participants from ADNI 1, Go, and 2, where patients should have full data regarding demographics, mini-mental state exam (MMSE), and whole brain volume measurements for baseline, 1 year, and 2 years.

**Results**: A total of 336 patients took part in this study, 184 (54.8%) of whom were men. In the studied group, 65 (19.3%), 150 (44.6%), and 121 (36%) were AD, MCI and NC, respectively. The mean change in brain volume for a 1-year interval was 1.52% ($\pm$2.15), and for a 2-year interval was 2.22% ($\pm$2.12). Only age significantly predicted the 2-year interval change in brain volume ($p= 0.009$), where one-year increase in age predicted a two-year interval brain volume loss by 0.06% (CI 0.02% to 0.10%).

**Conclusion**: Among the studied factors (age, gender and diagnosis), age was the only factor that significantly predicted the rate of whole brain volume loss with direct correlation between age and rate of volume loss at 2 years of observation.

## Introduction

Alzheimer disease (AD) is a neurodegenerative disorder marked by cognitive and behavioral impairment. It is the most common cause of dementia worldwide, and the 6th leading cause of death [1]. Pathologically, it is characterized microscopically by intracellular neurofibrillary tangles and extracellular amyloid protein deposits, contributing to senile plaques [2]. It is also characterized macroscopically by brain atrophy, which is a characteristic macroscopic

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consequence of AD pathology that also occurs to a lesser degree in normal aging process [3]. Another entity related to AD and considered to be a pre-Alzheimer's state is Mild Cognitive Impairment (MCI), an entity that involves subjects showing measurable memory deficits without meeting AD criteria [4]. Currently, there are no effective pharmacological therapies for reducing its severity and restoring the cognitive function [5].

The relationship between advancing age and brain volume was observed since the 19th century and probably earlier using data from autopsies [6]. With the use of imaging techniques, it was an easier process to assess changes in brain volume with aging [7]. The use of magnetic resonance imaging in determining brain volume was first described in 1988 and showed a decrease in normalized brain volume between the ages of 20 and 60 years in males by 1.6% per decade [8]. It is almost universally agreed that ageing is associated with brain volume atrophy, regardless of the presence of comorbid conditions (e.g. Alzheimer's disease) [9]. Most studies concerned with brain volume assessment with age are cross-sectional studies; thus, they cannot be used to judge the rate of brain volume change with age, especially in elderly patients.  In this study, we aim to find the change in whole brain volume in relation to age over 1-year and 2-year intervals', and the effect of having AD or MCI on this change.

**Methods**

**Participants**
Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI; adni.loni.usc.edu), which is a multicenter, prospective study that started in 2004, aiming to study Alzheimer's disease. It includes normal patients (controls), patients with minimal cognitive impairment, and patients with Alzheimer's disease. These patients underwent recurrent clinical assessments and investigational follow ups. In this study, our sample included three groups, namely controls, MCI, and AD patients. Normal controls (NC) had a mini-mental state examination (MMSE, a 30 point scale where higher score indicates better cognitive function), specifically, score between 24-30 (inclusive), a global clinical dementia rating (CDR, rating system addressing different aspects of cognition and its impairment ranging from zero; no impairment, 0.5 suspicious impairment and 1,2,3 indicating mild, moderate and severe impairment respectively), score of 0, and did not meet criteria for MCI or dementia. MCI participants had MMSE scores between 24-30 (inclusive), a memory complaint, evidence of objective memory loss as measured by education adjusted scores on the Wechsler Memory Scale Logical Memory II. In this modified version, free ADNI-D protocol and free recall of one short story (Story A) that consists of 25 bits of information were elicited immediately after it was read aloud to the subject and were obtained after a thirty-minute delay. The total bits of information from the story were recalled immediately (maximum score = 25). After that, the delay interval (maximum score = 25) was recorded and a retention score was calculated, where a CDR of 0.5 indicated absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and absence of dementia [10]. All AD subjects met National Institute of Neurological and Communication Disorders/Alzheimer's Disease and Related Disorders Association criteria for probable AD with a MMSE score between 20 and 26, a global CDR of 0.5 or 1, a sum-of-boxes CDR

of 1.0 to 9.0 (The CDR-SOB score is obtained by summing each of the domain box scores, with scores ranging from 0 to 18) [11]. We included participants from ADNI 1, Go, and 2. ADNI-1 started in 2004 with a 5 year duration goal and included a cohort of 200 elderly controls, 400 MCI, and 200 AD patients. With the end of ADNI-1 in 2009, another fund (ADNI-GO) extended the study for 2 more years and added 200 MCI patients to the original ADNI-1 cohort. In 2011, ADNI-2 started and it included the original cohort from ADNI-1 and ADNI-GO with the addition of 150 elderly control, 250 MCI, 150 late MCI, and 150 AAD patients [12]. Patients should have full data regarding demographics, MMSE, and whole brain volume measurements for baseline, 1 year, and 2 years. Whole brain volume measurement was done for each group using the methodology described in the ADNI MRI methods [13].

### Brain Volume Assessment

To adjust the baseline brain volume values, we assessed the percentage change in brain volume at one and two years according to the following equations:

- Brain volume change after 1 year = (baseline brain volume – brain volume after 1 year) / baseline brain volume
- Brain volume change after 2 years = (baseline brain volume – brain volume after 2 years) / baseline brain volume

### ADNI data

Clinical, biochemical, and imaging data of AD, MCI, and control groups were obtained from the ADNI database (adni.loni.usc.edu) on 11th of August 2017. The ADNI was launched in 2003 as a public-private partnership, led by the principal investigator Michael W. Weiner, MD. The primary goal of ADNI is to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be

combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org. We obtained baseline measurements for all the subjects who were included in this study for the previously mentioned parameters.

### Statistical Analysis

We used SPSS statistics (version 21.0, Chicago, USA) to conduct our analysis. Descriptive statistics was done using frequency (percentages) for nominal or ordinal variables and mean ($\pm$ standard deviation) for continuous variables. We first used the independent sample *t*-test to study gender differences in brain volume changes. Linear regression analysis was used to predict the change at 1-year and 2-year intervals change in brain volume, using age, gender, and diagnosis as predictors. Here, we report our results in the magnitude of change of the dependent variable (95% confidence interval) for a one-unit change in the predictors. A *p* value of $\leq 0.05$ represents a significant change.

### Results

A total of 336 participants were included in this study, 184 (54.8%) of whom were men. The mean age was 76.4 $\pm$6.61, 76.8 $\pm$7.08, and 75.8 $\pm$5.98 years for the whole cohort, men and women, respectively. In the studied groups, 65 (19.3%), 150 (44.6%), and 121 (36%) were AD, MCI and NC, respectively (Table1). The mean change in brain volume for a 1-year interval was 1.52% ($\pm$2.15), and for a 2-year interval was 2.22% ($\pm$2.12). There were no significant

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differences related to gender for any of the intervals. Table 1 summarizes the findings of this study regarding brain volume loss.

**Table 1: The findings of this study regarding brain volume loss**

|  | Diagnosis | %Mean ±SD | 95% CI |
|---|---|---|---|
| % of Brain volume change in 1st year | AD | 1.46±1.76 | -2.62-5.58 |
|  | MCI | 1.80±2.29 | -3.98-12.49 |
|  | NC | 1.25±2.12 | -4.69-11.22 |
|  | Total | 1.52±2.16 | -4.69-12.49 |
| % of Brain volume change in 2nd year | AD | 2.31±1.80 | -1.59-5.66 |
|  | MCI | 2.55±2.31 | -1.80-11.42 |
|  | NC | 1.88±2.02 | -1.55-12.60 |
|  | Total | 2.22±2.12 | -1.80-12.60 |

Detailed percentages (%) of brain volume changes in the 1st and 2nd years in Alzheimer's Disease (AD), Minimal Cognitive Impairments (MCI), and Normal Controls (NC). CI is confidence interval, SD is standard deviation

On the regression analysis of age, gender, and diagnosis, only age significantly predicted the 2-year interval change in brain volume (p= 0.009). Increase of age by one year predicted a more two-year interval brain volume loss by 0.059% (CI 0.015% to 0.10%), as detailed in Table 2.

**Table 2: Regression analysis of age and 1- and 2-year interval change in brain volume**

| Years | Variable | B | Sig. | 95% CI |
|---|---|---|---|---|
| 2- years interval | Diagnosis | -0.33 | .095 | -0.71 to 0.06 |
|  | Gender | -0.15 | .605 | -0.71 to 0.42 |
|  | Age | -0.06 | .009 | -0.10 to -0.02 |
| 1-year interval | Diagnosis | -0.19 | 0.29 | -0.54 to 0.16 |
|  | Gender | 0.07 | 0.78 | -0.44 to 0.59 |
|  | Age | -0.04 | 0.07 | -0.07 to 0.01 |

B represents the change in the percentage of brain volume with 2 and 1 year change, respectively. Sig: statistical significant (p value), CI: confidence interval

**Discussion**

MRI permits in vivo quantification of brain volume that can be used as a biomarker of either aging or disease progression [14]. In this study that included AD, MCI, and NC (all >65 years of age), we found that the only factor affecting change in brain volume over 2-year interval is age. The increase in age by one year will result in a predicted decrease in whole brain volume atrophy rate by 0.06% from its baseline. As an example, a 75-year-old patient is expected to have brain atrophy rate after 2 years (when he becomes 77 years) of about 0.6% higher than his rate when he was 65 years old (10-year interval, so for each 1000ml of brain volume, he will lose 6 ml more). MRI volume measurements has a primary role in identifying and assessing volume changes in characteristic locations, particularly, hippocampal volume, which has a great potential as a marker for AD [15], but it can also be used to assess whole brain volume, which may represent an aging biomarker. Studies of older populations showed higher rates of brain atrophy. One study of normal elderly (74-87 years of age) showed annual atrophy rate of 2.1% (± 1.6%) [16]. Another cross-sectional study showed the rate of annual brain atrophy to be age dependent. It varied from 0.2% to 0.52% at 35 and 75 years of age, respectively [17]. Specific brain regions atrophy assessment was approached by other studies. A community cohort of 1,172 healthy adults (65-82 years old) was longitudinally followed for 4 years. The study showed a global annualized rate of grey matter loss of -4.0 cm3/year (-0.83%/year) [18]. Recent studies

suggest that changes in brain volume and specifically grey matter differ according to brain regions [19]. Data taken from the Leiden longevity study showed that the grey matter volume decreases with age in networks containing subcortical structures, sensorimotor structures, posterior, and anterior cingulate cortices, while grey matter volume in temporal, auditory, and cerebellar networks remains relatively unaffected with advancing age [20]. Two recent large cohort studies were analyzed. The first was acquired at the Medical Prevention Center (MPCH) in Hamburg, Germany. The second cohort was taken from the Open Access Series of Imaging Studies (OASIS). Brain Parenchyma (BP), Grey Matter (GM), White Matter (WM), Corpus Callosum (CC), and thalamus volumes were calculated. The mean absolute difference between brain volume loss/year across the age range of 35-70 years was 0.02% for BP, 0.04% for GM, 0.04% for WM, 0.11% for CC, and 0.02% for the thalamus [21, 22]. A longitudinal study of patients with AD showed annual atrophy rates of almost 2% [23]. Data is conflicting with regard to whether the rate of atrophy is faster in AD compared to MCI or not [24]. In a longitudinal study, authors concluded that there is no difference in brain atrophy acceleration due to AD or MCI compared to control, which would suggest a long period of transition to pathological losses seen clinically in AD [25]. However, another longitudinal study showed a statistically significant decline in grey matter volume in AD compared to MCI and normal population. It also showed a correlation

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between brain atrophy and clinical cognitive decline [25]. The data analyzed in our study showed no significant change in brain volume loss rates between AD, MCI or NC. This may be explained by the insignificance of total brain volume measurement in such clinical setting, the short duration of observation (2 years, this was the only period interval with complete data available), early disease stage, or insensitive tools of measurement. Future studies should focus on specific regions in the brain (e.g. hippocampus) and follow patients for longer durations. The different average change in volume loss in the three studied groups over the first and second years (1.52% and 2.22%, respectively) compared to previous studies may be explained by the different methods of measurement (MRI vs autopsies), nature of study (longitudinal vs cross sectional), and population (age and gender distribution as well as socioeconomic and comorbidities) studied. The strength of this study is related to its longitudinal follow up, the strict definitions used to select patients, the good quality of data available for study group. Its limitation is related mainly to short duration of follow up and the relatively small number of subjects studied for such a common medical problem.

## Conclusion

In this cohort derived from the ADNI data base, there was no significant difference over one and two years of observation in the changes in total brain volume assessed by MRI in NC, MCI or AD. The only factor that was significant as a predictor of rate of whole volume loss was the age of onset of measurement with direct correlation between the age and rate of volume loss.

(www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study was coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data were disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

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# أثر العمر على حجم الدماغ عند كبار السن ومرضى الضعف البسيط في القدرات الذهنية و مرضى الخرف (مرض الزهايمر). دراسة مستقبلية شعاعية مستمدة من قاعدة بيانات المبادرة الشعاعية في دراسة مرضى الزهايمر

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## الملخص

**مقدمه:**يعد مرض الزهايمر من أكثر الأسباب شيوعا للخرف في العالم. ويتميز هذا المرض بضمور في الدماغ كما ثبت ذلك تشريحياً وعن طريق تصوير الدماغ . مع العلم أن ضمور الدماغ يحصل طبيعياً مع التقدم في العمر. في هذه الدراسة، نسعى إلى معرفة مدى ضمور الدماغ بواسطة التصوير بالرنين المغناطيسي بعد عام (MCI)، ونظرائهم الطبيعيين من نفس العمر. طريقه البحث:

**الطرق :**قمنا بدراسة قاعدة بيانات المبادرة الشعاعية في دراسة مرضى الخرف (الزهايمر) المتوفرة في قاعدة البيانات المفتوحة (ADNI) . في هذا البحث، تمت دراسة ثلاث مجموعات من مرضى الخرف (الزهايمر) وعند المرضى ذوي الضعف البسيط في القدرات الذهنية (MCI)، والطبيعيين. ضمت الدراسة المرضى من بداية جمع قاعدة البيانات(ADNI)، وفي مراحلها (GO،1 ،2) وتمت دراسة المرضى الذين كانت معلوماتهم السريرية والإشعاعية كاملة في فترات البداية، وبعد سنة، و بعد سنتين.

**النتائج:** تم دراسة 336 شخصاً، وكان 184 (54.8%) منهم ذكوراً. توزع هؤلاء بين 19.3% مرض الزهايمر، 44.6% MCI و36% طبيعيين. معدل التغير في حجم الدماغ في السنة الأولى كان قليلاً بمقدار 1.52%   (2.15±) وبعد سنتين 2.22% (2.12±).النتائج: بعد التحليل، تبين أن العامل

الوحيد الذي يتنبأ بمقدار الضمور بعد سنتين من بين العوامل التي تمت دراستها (الجنس، العمر، التشخيص) هو العمر، حيث أن زيادة سنة واحدة في العمر منذ بدء الدراسة تنبأت بزيادة الضمور بمقدار 0.06%.

**الكلمات الدالة:**مرض الزهايمر ،حجم الدماغ ، ضمور الدماغ ، تقدير الحجم بالتصوير المغناطيسي

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