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Sluimer, J.D.

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Chapter 3

Whole-brain atrophy and cognitive decline: A longitudinal MRI study of memory clinic patients

Radiology 2008

J.D. Sluimer
W.M. van der Flier
G.B. Karas
N.C. Fox
Ph. Scheltens
F. Barkhof
H. Vrenken

Abstract

Purpose: To prospectively determine the whole-brain atrophy rate in mild cognitive impairment (MCI) and Alzheimer's disease (AD) and its association with cognitive decline, as well as investigate the risk of progression to dementia in initially non-demented patients based on baseline brain volume and whole-brain atrophy rate.

Materials & Methods: Our study had institutional ethical committee approval; written informed consent was obtained from all participants. We included 65 patients with AD (age-range, sex(f/m): 52-81y, 38/27), 45 patients with MCI (56-80y, 22/23), 27 patients with subjective complaints (50-87y, 12/15) and 10 normal controls (53-80y, 6/4). Two MR scans were acquired, with an average interval of 1.8 ± 0.7 years. Baseline brain volume and whole-brain atrophy rates were measured from 3D T1-weighted MR imaging (1.0T; single slab, 168 slices; matrix size 256x256; FOV 250mm; voxel size 1x1x1.5 mm; TR=15ms; TE=7ms; TI=300ms; flip angle 15°). Associations were assessed using partial correlations. Cox proportional hazards models were used to estimate risk of developing dementia.

Results: Baseline brain volume was lowest in AD, but did not differ significantly between the MCI, subjective complaints and control groups ($p > 0.38$). Whole-brain atrophy rates were higher in AD (mean \pm SD $-1.9 \pm 0.9\%/y$) than MCI ($-1.2 \pm 0.9\%/y$; $p = 0.003$), who in turn had higher whole-brain atrophy rates than patients with subjective complaints ($-0.7 \pm 0.7\%/y$; $p = 0.03$) and controls ($-0.5 \pm 0.5\%/y$; $p = 0.05$). Whole-brain atrophy rate correlated with annualized mini-mental state examination (MMSE) change ($r = 0.48$, $p < 0.001$), while baseline volume did not ($r = 0.11$, $p = 0.22$). Cox proportional hazard models showed that -after correction for age, sex, and baseline MMSE- a higher whole-brain atrophy rate was associated with an increased risk of progression to dementia (highest vs lowest tertile (hazard ratio 3.6, 95% confidence interval 1.2-11.4)).

Conclusions: Whole-brain atrophy rate was strongly associated with cognitive decline. In non-demented participants a high whole-brain atrophy rate was associated with an increased risk of progression to dementia.

Introduction

Alzheimer's disease is characterised by an insidious onset of progressive cognitive decline. The term mild cognitive impairment is used to describe patients who do not fulfil clinical criteria for dementia, but who do have objective evidence of memory deficits. MCI patients are at an increased risk of developing AD¹; however, not all patients diagnosed with MCI progress to AD, some develop another type of dementia, while others improve or remain clinically stable.^{2,3}

Structural MR imaging allows tissue loss (atrophy) to be assessed *in vivo*.⁴ Many studies in AD focussed on the medial temporal lobe, known to be affected early in the disease.^{5,8} However, development of atrophy is not limited to this region. Neocortical loss and enlargement of the ventricles have been reported at an early stage.^{9,10} It has been suggested that whole-brain atrophy rate is more sensitive to the earliest disease changes than brain volume measurement at a single time point.^{11,14} Reported whole-brain atrophy rates in AD range from 1% to 4% per year,^{15,18} while healthy elderly have (age-related) atrophy rates ranging from 0.2 % to 0.7 % per year.^{19,20} Relatively few studies have addressed the issue of whole-brain atrophy rates across the cognitive spectrum of normal cognition, MCI and AD.^{21,23}

Thus, the purpose of this study was to prospectively determine the whole-brain atrophy rate in mild cognitive impairment and Alzheimer's disease and its association with cognitive decline, as well as to investigate the risk of progression to dementia in initially non-demented patients based on baseline brain volume and whole-brain atrophy rate.

Material and methods

Patients

Baseline clinical assessment

The study was approved by the institutional ethical review board. All participants (or caregivers) gave written informed consent. We included 65 patients with AD (age-range, sex (f/m): 52-81y, 38/27), 45 patients with MCI (56-80y, 22/23), and 27 patients with subjective complaints (50-87y, 12/15). Patients underwent a standardized clinical assessment including medical history, physical and neurological examination, psychometric evaluation, and brain MRI. The mini-mental state examination (MMSE) was used as a measure of general cognitive function²⁴). Diagnoses were established during a multidisciplinary consensus meeting according to the Petersen criteria for MCI²⁵ and the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) criteria for probable AD²⁶. When all clinical investigations were normal (i.e. MCI criteria were not fulfilled), patients were considered to have subjective complaints. Additionally, we included 10 normal individuals without cognitive complaints (controls (53-80y, 6/4)), recruited from caregivers, who were willing to undergo the same diagnostic procedure as patients attending our memory clinic.

Clinical assessment at follow-up

Non-demented participants (MCI and subjective complaints) visited the memory clinic annually. Diagnostic classification was re-evaluated at follow-up. The clinical diagnosis of dementia was determined according to published consensus criteria^{25,29}. Within the MCI group, 17 patients had remained stable, 23 progressed to AD, two to fronto-temporal lobar degeneration (FTLD)²⁷, two to vascular dementia (VaD)²⁸ and one to dementia with Lewy bodies (DLB)²⁹. Within the group of patients with subjective complaints, three patients progressed to MCI, three to AD and one to FTLD while 20 patients remained stable. All normal controls without complaints remained stable.

MRI and Evaluation

Between 2004 and 2006 all patients attending our memory clinic were invited for a repeat MR scan. Follow-up time is defined as time between the two MRI scans (mean interval 1.8 years, standard deviation 0.7; range 11m-4y2m). MR imaging was performed on a 1.0-T Siemens Magnetom Impact Expert System (Siemens AG, Erlangen, Germany) and included coronal T1-weighted 3D MPRAGE volumes (magnetization prepared rapid acquisition gradient echo; single slab, 168 slices; matrix size 256x256; FOV 250x250mm; voxel size 1x1x1.5 mm; TR=15ms; TE=7ms; TI=300ms; flip angle 15°). A total of 159 patients agreed to undergo 2 MR scans (71 AD, 49 MCI, 29 subjective complaints, 10 controls). Participants were included only: 1. if they had two scans of adequate quality, performed on the same scanner using the same imaging protocol. 2. if non-neurodegenerative pathology that could explain the cognitive impairment was present, as judged by one radiologist with 15 years experience in dementia field (FB). 3. if fully-automated SIENA(X) (Structural Image Evaluation, using Normalisation, of Atrophy, (X-sectional)) processing output did not yield errors, as checked for errors by a rater who was blinded to the diagnosis (JS, 4 years experience in dementia field, MR imaging and image analysis). Consequently we excluded 12 patients; two because of movement artefacts in the original MRI data, seven participants had non-neurodegenerative pathology associated with cognitive impairment (one hydrocephalus, one tumor, one hemorrhage, and four patients fulfilled NINDS-AIREN criteria for vascular dementia). Finally, three scans were excluded from analysis, because of remaining non-brain tissue after processing. A total of 147 participants were included (65 AD, 45 MCI, 27 subjective complaints, 10 controls)

Normalized baseline brain volume (NBV) and percentage brain volume change (PBVC) between two time-points were measured from the MPRAGE images using SIENAX, and SIENA, two fully automated techniques that are part of FSL (for a detailed explanation see: www.fmrib.ox.ac.uk/analysis/research/siena).^{30,31}

Whole-brain atrophy rate was measured with SIENA. Briefly, the brain was extracted using the brain extraction tool.³¹ Compared to standard SIENAX and SIENA, the procedure to remove non-brain tissue was slightly modified, because the brain extraction tool often leaves substantial amounts of non-brain tissue

when using a single slab 3D MPRAGE sequence, while also removing cortex in some areas.³² To remove all non-brain tissue without losing cortex, we incorporated registration of a template mask to the individual scan. After brain extraction the two brain images were aligned to each other, using the skull images to constrain the registration scaling. Both brain images were resampled into the space halfway between the two. Next, tissue-type segmentation was performed in order to find brain / non-brain edge points, and for each edge point perpendicular edge displacement between baseline and repeat scan was measured. The mean edge displacement was automatically converted into a global estimate of PBVC between the two time points

Baseline brain volume, normalized for subject head size, was measured with a cross-sectional modification of SIENA called SIENAX. Briefly, after brain extraction, tissue-type segmentation with partial volume estimation was carried out in order to calculate total volume of brain tissue. In addition, to correct for interindividual differences in head size, a volumetric scaling factor was obtained by registering the brain image to MNI152 space, using an affine transformation (i.e., a linear transformation with 12 degrees of freedom), and using the skull to constrain the registration scaling. Baseline brain volume, normalized for subject head size, was then obtained by multiplying the volume of brain tissue by the volumetric scaling factor. We used the baseline normalized brain volume as a cross-sectional measure, and whole-brain atrophy rate (PBVC) as a longitudinal measure of atrophy.

Statistical Analysis

Statistical analysis was performed with SPSS 12.0 (2003, Chicago, Illinois). PBVC and change in MMSE were annualized by dividing by the intermediate time interval between observations in years. Diagnostic groups were compared with chi-squared tests for sex. For continuous variables (age, MMSE, MMSE change, MR scan interval, normalized baseline brain volume, whole-brain atrophy rate) we used analysis of variance (ANOVA), with age and sex as covariates. Post-hoc comparisons were performed using Bonferroni tests. Box-and-whisker plots of baseline brain volume and whole-brain atrophy rate, by diagnostic group were constructed. Associations of baseline brain volume and whole-brain atrophy rate with MMSE and MMSE change were assessed using

partial correlations, corrected for age and sex. Scatter plots of baseline brain volume and whole-brain atrophy rate versus annual change in MMSE were created. Within the group of initially non-demented participants we assessed the predictive value of baseline brain volume and whole-brain atrophy rate, by using Cox proportional hazards models, which account for variability in length of follow-up. Among those initially non-demented, baseline brain volume and whole-brain atrophy rate were categorized into tertiles and entered as categorical variables in the model. Hazard ratios (HRs) with 95% confidence interval (CI) are presented. First (model 1), unadjusted HRs are presented. In model 2, sex and age were corrected for, and in model 3 baseline MMSE was added as an additional covariate. Main outcome was progression to dementia, second outcome was progression to AD, which excludes six cases who developed a different kind of dementia. Time-to-event curves were constructed with the Kaplan-Meier method. Statistical analysis was performed by JS and WF. Statistical significance was set at $p < 0.05$.

Results

Brain volume, Whole-brain atrophy rate

There were group differences for both baseline brain volume and whole-brain atrophy rate (Table 1, Figure 1). Post-hoc Bonferroni-corrected tests illustrated that brain volume at baseline was lowest for the AD group (vs MCI $p = 0.09$; vs subjective complaints $p < 0.001$; vs controls $p < 0.01$), but the MCI group did not differ from either the subjective complaints ($p = 0.38$) or control groups ($p = 0.48$). No difference between patients with subjective complaints and controls was found ($p = 1.00$).

By contrast, annualized whole-brain atrophy rates (PBVC) did not only differentiate the AD group from all other groups, but also showed differences between the other groups. AD patients had higher whole-brain atrophy rates compared to MCI ($p = 0.003$), who in turn had higher whole-brain atrophy rates compared to subjective complaints ($p = 0.025$) and controls ($p = 0.05$). No difference was found between subjective complaints and controls ($p = 1.00$) (Figure 2).

Table 1. Demographics and clinical variables

	Controls	Subjective complaints	MCI	AD	F _{df,df} (p-value)
Number of participants	10	27	45	65	
Number converted	10 stable	20 stable 3 MCI 3 AD 1 other	17 stable 23 AD 5 other	-	
Age-at-diagnosis (y)	69 (7)	66 (9)	71 (6)	67 (8) ^c	3.0 _{3,143} (0.03)
Sex (f/m)	6 / 4	12 / 15	22 / 23	38 / 27	2.1 _{3,3} (0.56)
MMSE baseline*	28 (2)	28 (1)	26 (3) ^b	22 (4) ^{f,g,h}	27.0 _{3,141} (<0.001)
MMSE annual decline*+	0.3 (0.9)	-0.2 (1.4)	-1.5 (2.5) ^{a,b}	-2.1 (2.1) ^{d,g}	7.9 _{3,128} (<0.001)
MR scan interval (y) *	2.3 (0.5)	1.7 (0.9)	1.9 (0.7)	1.7 (0.6)	2.5 _{3,141} (0.06)
Normalized baseline brain volume (ml) *	1541 (99)	1536 (91)	1483 (78)	1453 (88) ^{d,g}	8.0 _{3,141} (<0.001)
Annualized whole-brain atrophy rate (%/y) *	-0.5 (0.5)	-0.7 (0.7)	-1.2 (0.9) ^{a,b}	-1.9 (0.9) ^{f,g,e}	18.0 _{3,141} (<0.001)

Table 1. Group difference for sex (f/m) was calculated with Pearson Chi-Square. Other data in this table is displayed as mean (sd). F-value is displayed with degrees of freedom for contrast and error, respectively. Differences between groups were assessed using ANOVA (*age and sex as covariates, post-hoc Bonferroni correction p<0.05). + available for n=134; a p<0.05 compared to controls; b p<0.05 compared to subjective complaints; c p<0.05 compared to MCI; d p<0.01 compared to controls; e p<0.01 compared to MCI; f p<0.001 compared to controls; g p<0.001 compared to subjective complaints; h p<0.001 compared to MCI; MCI=mild cognitive impairment; AD=Alzheimer's disease; MMSE=mini-mental state examination

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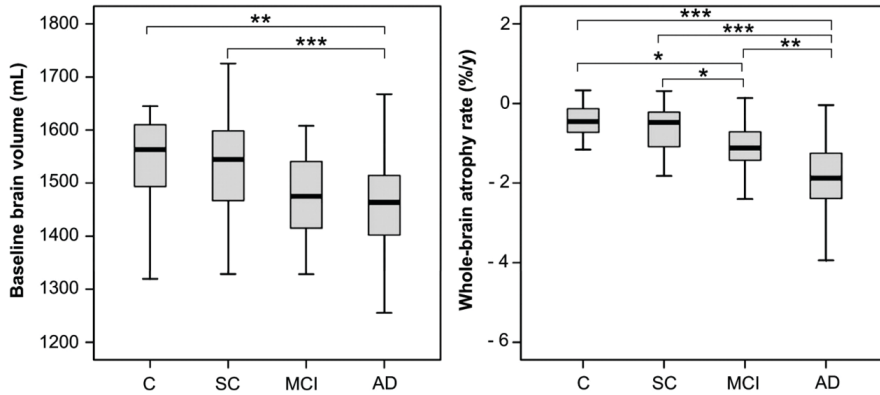


Figure 1. Box-and-whisker plot of (left) baseline brain volume and (right) whole-brain atrophy rate, by diagnostic group (C=controls, SC=subjective complaints, MCI = mild cognitive impairment, AD = Alzheimer's disease). Horizontal line inside box is median value. Differences between groups were assessed using ANOVA (age and sex as covariates, post-hoc Bonferroni correction), and are indicated by asterisks:

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

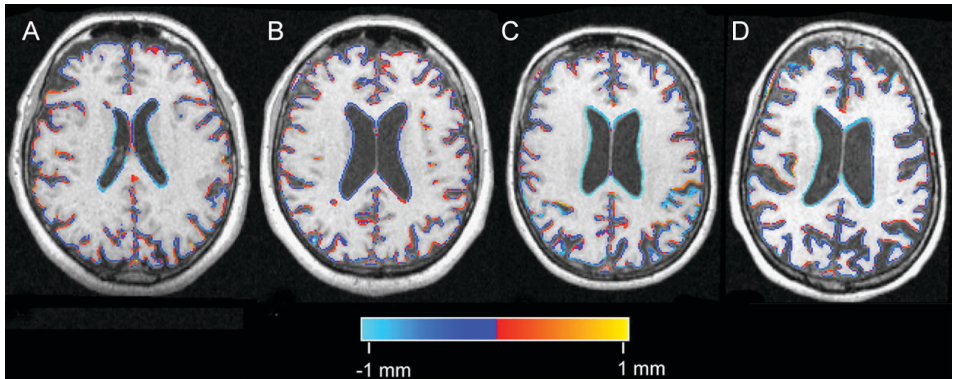


Figure 2. Four examples of individual edge-displacement maps, overlaid on baseline axial MR images. Dark-blue to light-blue represents mild to severe local contraction respectively, which implies atrophy. Red to yellow indicates mild to severe expansion of brain tissue. Note that for display purposes, edge motion was truncated at 1 mm in this figure. (A) patient with subjective complaints (age, normalised baseline brain volume, whole-brain atrophy rate: 74 y, 1471mL, -0.7%/y), (B) a patient with Mild Cognitive Impairment, who did not progress to AD (80y, 1607mL, -0.6%/y), (C) a patient with Mild Cognitive Impairment, who progressed to AD (67 y, 1548 mL, -1.9 %/y) and (D) a patient diagnosed with Alzheimer's disease at baseline (63 y, 1286mL, -4.2%/y).

Cognitive decline

To investigate whether baseline brain volume and whole-brain atrophy rate reflected cognitive decline, we assessed associations with baseline MMSE and annualized MMSE change (Figure 3). Partial correlations corrected for age and sex showed that across the whole sample, baseline brain volume correlated with baseline MMSE ($r=0.32$, $p<0.001$), but not with annualized change in MMSE ($r=0.11$, $p=0.22$). Whole-brain atrophy rate (PBVC) however, was associated with both baseline MMSE ($r=0.48$, $p<0.001$) and change in MMSE ($r=0.48$, $p<0.001$). Further evaluation of correlations within diagnostic groups showed that baseline brain volume was not associated with either MMSE or MMSE change within any of the groups. By contrast, whole-brain atrophy rate was associated both with MMSE and MMSE change within the AD group ($r=0.37$, $p<0.01$; $r=0.34$, $p<0.01$). Within the MCI group whole-brain atrophy rate was associated with MMSE change ($r=0.33$, $p<0.05$) but not with baseline MMSE ($r=0.09$, $p=0.61$). No such associations were found among patients with subjective complaints or controls.

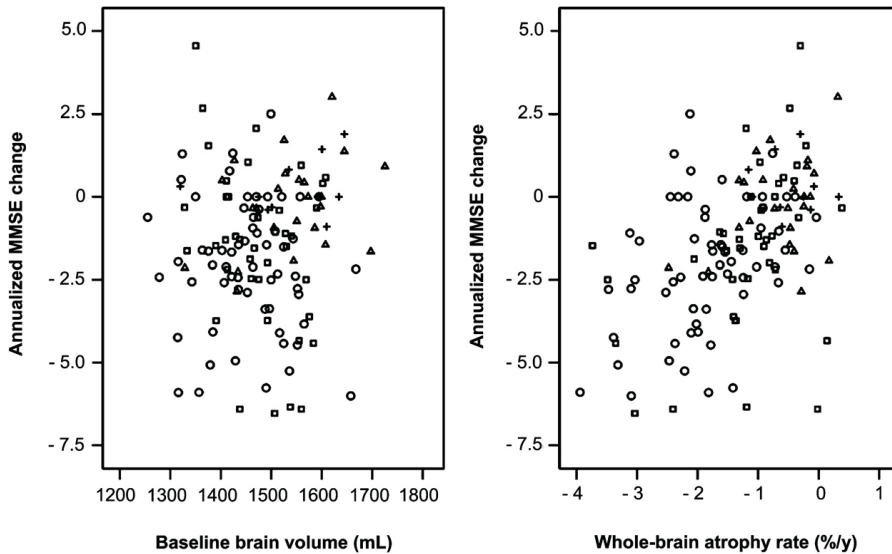


Figure 3. Scatterplots of (left) baseline brain volume and (right) whole-brain atrophy rate by annual change in mini-mental state examination (MMSE). Data for the entire spectrum of cognitive decline are presented. No association between baseline brain volume and annual MMSE decline was found (Figure 3a; partial correlation, correcting for age and sex: $r=0.11$, $p=0.22$). By contrast, whole-brain atrophy rate was associated with annualized MMSE change (Figure 3b; $r=0.48$, $p<0.001$). Subsequent evaluation of correlations within diagnostic groups showed that whole-brain atrophy rate was associated with annualized MMSE change within the AD group ($r=0.34$, $p<0.01$), and within the MCI group ($r=0.33$, $p<0.05$). No associations were found among normal controls or subjective memory complaints.

+ = normal controls; Δ = subjective memory complaints; \square = MCI; \circ = AD

Prediction of Progression to Dementia

Finally, we assessed the predictive value of baseline brain volume and whole-brain atrophy rate for progression to dementia in initially non-demented patients (n=82), using tertiles of MRI measures (Figure 4, Table 2). Baseline brain volumes were $1603\pm 40\text{mL}$ in the large, $1512\pm 26\text{mL}$ in the middle, and $1410\pm 46\text{mL}$ in the small tertile. Whole-brain atrophy rates (%/y) were -0.2 ± 0.2 in the lowest, -0.8 ± 0.2 in the moderate and -1.8 ± 0.8 in the high tertile. Compared with a large baseline brain volume, a small volume was associated with a threefold increased risk of progression to dementia in the unadjusted model. However, after adjusting for age, sex and baseline MMSE, this effect largely disappeared. Patients in the moderate whole-brain atrophy rate tertile had a twofold - though not significantly - increased risk of progression to dementia, in comparison with patients with a low whole-brain atrophy rate. A high whole-brain atrophy rate (highest tertile) was associated with a more than fourfold increased risk of progression to dementia. These results remained significant after correction for age, sex and baseline MMSE. When the analysis was restricted to progression to AD (i.e. excluding the six patients who progressed to another type of dementia), all results were essentially unchanged: corrected for age, sex and baseline MMSE (model 3), smaller baseline brain volumes were associated with a modest - although not significantly - increased risk (middle: $\text{HR}(95\%\text{CI})= 1.8(0.5-6.6)$; small: $\text{HR}(95\%\text{CI})= 1.9(0.5-7.3)$), while whole-brain atrophy rate was associated with a more strongly increased risk of progression to AD (moderate: $\text{HR}(95\%\text{CI})= 1.3(0.4-4.8)$; high: $\text{HR}(95\%\text{CI})= 3.5(1.1-11.2)$).

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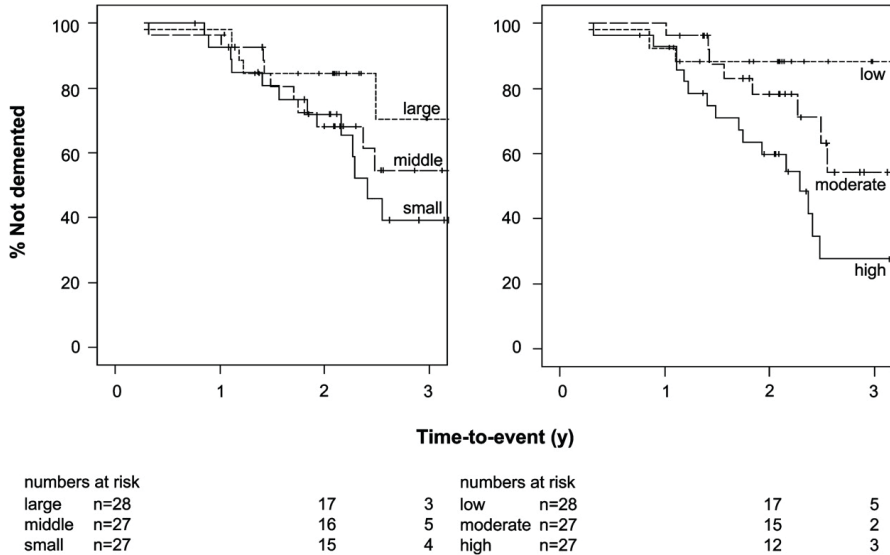


Figure 4. Kaplan-Meier curve of time-to-conversion in initially non-demented patients (n=82) depends on (left) baseline brain volume and (right) whole-brain atrophy rate. Baseline brain volume and whole-brain atrophy rate were divided into tertiles. Numbers at risk are displayed below graph. Participants reaching end of follow-up period without progression to dementia were censored. + = censored

Table 2. Hazard ratios (HR) and 95 % confidence interval (CI) of progression to dementia

HR (CI)	Model 1: univariate	Model 2: age, sex	Model 3: age, sex, baseline MMSE
Baseline brain volume (mL)			
Large	1 (-)	1 (-)	1 (-)
Middle	1.7 (0.6 - 5)	1.7 (0.5 - 5.2)	1.2 (0.4 - 3.9)
Small	3 (1.1 - 8.4)	2.9 (0.9 - 9)	1.6 (0.5 - 5.1)
Whole-brain atrophy rate (%/y)			
Low	1 (-)	1 (-)	1 (-)
Moderate	2.2 (0.7 - 7.2)	2 (0.6 - 7)	1.8 (0.5 - 6.1)
High	4.6 (1.5 - 13.6)	4.3 (1.4 - 13.5)	3.6 (1.2 - 11.4)

Table 2. Baseline brain volume and whole-brain atrophy rate were categorized into tertiles. Data are shown as Hazard ratios (HRs) with 95% confidence interval (CI). In model 1 unadjusted HRs are presented. In model 2 sex and age were corrected for, and in model 3 baseline MMSE was added as an additional covariate.

Discussion

Our study results show that while baseline brain volume was significantly lower in AD than in patients with subjective complaints and controls, it did not distinguish AD from MCI, nor could MCI be distinguished from subjective complaints and controls using baseline brain volume. By contrast, whole-brain atrophy rates were able to separate AD from MCI and MCI from subjective memory complaints and controls, illustrating that whole-brain atrophy rate is more sensitive than cross-sectional brain volume. The clinical relevance of this marker was demonstrated by the association of whole-brain atrophy rate with baseline cognition and rate of cognitive decline. Finally, for initially non-demented patients a high whole-brain atrophy rate was associated with increased risk of progression to dementia.

Our results confirm previous studies showing an increased whole-brain atrophy rate in AD versus controls. Our control group had a whole-brain atrophy rate of 0.5 % per year, which is in the middle of the previously reported range of rates of 0.2 % to 0.7 % per year.^{19,33} The AD patients had an annualized whole-brain atrophy rate of 1.9 %, almost four fold higher than controls. This is similar to previously reported rates in AD which are most typically around 2 % per year^{15,34}, although reported whole-brain atrophy rates in AD range from 1 % to 4 %, probably depending on the characteristics of the AD population, and method of atrophy rate calculation.^{17,35-37} We extend those earlier findings showing that while there was no difference in baseline brain volume, the whole-brain atrophy rate for the MCI group with 1.2 % per year was twice higher than among controls. This value is somewhat higher than the 0.7 % per year observed in a previous study.²¹ That study used BSI (boundary shift integral) to assess whole-brain atrophy, and is the only other study that assessed the risk of progression to dementia in the non-demented. They report a slightly increased risk of progression to dementia. Two other studies used brain segmentation to measure whole-brain atrophy rates.^{22,23} One of these studies assessed association of whole-brain atrophy rates with age, but not with cognitive decline.²² Both studies did not assess risk of progression to dementia. Our study adds to these previous observations by investigating a large cohort, recruited in a clinical setting, that covers the entire cognitive spectrum. We have used a well defined, easily accessible, fully automated

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atrophy measurement technique. Furthermore, we used the MMSE, the most commonly used clinical cognition test, to check for associations with whole-brain atrophy rates. Finally, we assessed the risk of progression to dementia, and found a more than three-fold risk of progression to dementia for participants with a higher rate of atrophy.

Whole-brain atrophy rate was more sensitive than baseline brain volume in distinguishing the diagnostic groups. Whole-brain atrophy rate showed a clear distinction between groups, while baseline brain volume could only distinguish AD. A higher sensitivity of longitudinal atrophy in the detection of subtle differences in whole-brain and localized atrophy rates has been reported previously in AD and other neurodegenerative disease.^{38,40} The higher sensitivity of whole-brain atrophy rate can in part be attributed to the fact that when a subject is compared with him/herself instead of with a standard brain template, the confounding influence of inter-individual variability is reduced, reducing the measurement error.

Among non-demented patients, a higher whole-brain atrophy rate was associated with a greater risk of progression to dementia. A small brain volume was associated with a threefold increased risk of progression to dementia, although this effect largely disappeared when correcting for age, sex, and baseline MMSE. By contrast, a high whole-brain atrophy rate was associated with a more than fourfold increased risk of progression to dementia, which remained significant after correcting for age, sex and baseline MMSE.

Our study included the entire cognitive spectrum: patients with AD and MCI, patients with subjective complaints (who in fact can be considered normal at baseline, since all baseline clinical investigations were normal) and individuals without complaints. No differences were found between patients with subjective complaints and controls. Pooling these two groups would not have altered the results of this study. Furthermore we included a relatively large number of participants from one center. All participants have been carefully defined using a standardized diagnostic battery. As a consequence, they are characterized in a uniform manner and the diagnosis was determined by a multidisciplinary team. MR imaging was always performed on the same scanner using the same protocol.

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A limitation of our study is that MR imaging of our participants was available for only two time points. In future studies, more than two MR scans per patient could be obtained to increase power and sensitivity, and to monitor the course of the disease. Furthermore, since no post mortem verification of diagnosis was available –which is considered the gold standard for diagnosing AD- we cannot exclude the possibility that some of our AD patients were misdiagnosed. However, all patients fulfilled NINDS-ADRDA clinical criteria for probable AD, which was confirmed both at baseline and at follow-up in multidisciplinary consensus meetings.

Our study confirms that whole-brain atrophy rate discriminates between diagnostic groups, better than cross-sectional brain volume. The clinical relevance of whole-brain atrophy rate is demonstrated by the association with cognition and cognitive decline. Since individuals with higher whole-brain atrophy rate had greater risks of progression to dementia, repeat MRI scans may be helpful in the diagnostic work-up of patients suspected of dementia.

Reference list

1. Petersen RC, Doody R, Kurz A et al. - Current concepts in mild cognitive impairment. - Arch Neurol 2001 Dec;58(12):1985-92.
2. Gauthier S, Reisberg B, Zaudig M et al. - Mild cognitive impairment. - Lancet 2006 Apr 15;367(9518):1262-70.
3. Visser PJ, Kester A, Jolles J, Verhey F. - Ten-year risk of dementia in subjects with mild cognitive impairment. - Neurology 2006 Oct 10;67(7):1201-7.
4. Scheltens P, Fox N, Barkhof F, De CC. - Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. - Lancet Neurol 2002 May;1(1):13-21.
5. Mungas D, Reed BR, Jagust WJ et al. - Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. - Neurology 2002 Sep 24;59(6):867-73.
6. Jack CR, Jr., Petersen RC, Xu Y et al. - Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. - Neurology 2000 Aug 22;55(4):484-89.
7. Rusinek H, De SS, Frid D et al. - Regional brain atrophy rate predicts future cognitive decline: 6-year longitudinal MR imaging study of normal aging. - Radiology 2003 Dec;229(3):691-6.
8. Tapiola T, Pennanen C, Tapiola M et al. - MRI of hippocampus and entorhinal cortex in mild cognitive impairment: A follow-up study. - Neurobiol Aging 2006 Nov 9.
9. Karas GB, Scheltens P, Rombouts S et al. - Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. Neuroimage 2004; 23:708-716.
10. Kaye JA, Moore MM, Dame A et al. - Asynchronous regional brain volume losses in presymptomatic to moderate AD. - J Alzheimers Dis 2005 Sep;8(1):51-6.
11. Fotenos AF, Snyder AZ, Girton LE, Morris JC, Buckner RL. - Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. - Neurology 2005 Mar 22;64(6):1032-9.
12. Freeborough PA, Fox NC. - The boundary shift integral: an accurate and robust measure of cerebral volume changes from registered repeat MRI. - IEEE Trans Med Imaging 1997 Oct;16(5):623-9.
13. Preboske GM, Gunter JL, Ward CP, Jack CR. - Common MRI acquisition non-idealities significantly impact the output of the boundary shift integral method of measuring brain atrophy on serial MRI. Neuroimage 2006; 30:1196-1202.
14. Smith SM, Zhang Y, Jenkinson M et al. - Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. - Neuroimage 2002 Sep;17(1):479-89.

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15. Schott JM, Price SL, Frost C, Whitwell JL, Rossor MN, Fox NC. Measuring atrophy in Alzheimer disease - A serial MRI study over 6 and 12 months. *Neurology* 2005; 65:119-124.
16. Fox NC, Scahill RI, Crum WR, Rossor MN. - Correlation between rates of brain atrophy and cognitive decline in AD. - *Neurology* 1999 May 12;52(8):1687-9.
17. Jack CR, Shiung MM, Gunter JL et al. Comparison of different MRI brain atrophy, rate measures with clinical disease progression in AD. *Neurology* 2004; 62:591-600.
18. Wang D, Chalk JB, Rose SE et al. - MR image-based measurement of rates of change in volumes of brain structures. Part II: application to a study of Alzheimer's disease and normal aging. - *Magn Reson Imaging* 2002 Jan;20(1):41-8.
19. Enzinger C, Fazekas F, Matthews PM et al. Risk factors for progression of brain atrophy in aging - Six-year follow-up of normal subjects. *Neurology* 2005; 64:1704-1711.
20. Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. - A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. - *Arch Neurol* 2003 Jul;60(7):989-94.
21. Jack CR, Shiung MM, Weigand SD et al. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnesic MCI. *Neurology* 2005; 65:1227-1231.
22. Fotenos AF, Snyder AZ, Girton LE, Morris JC, Buckner RL. - Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. - *Neurology* 2005 Mar 22;64(6):1032-9.
23. Mungas D, Harvey D, Reed BR et al. Longitudinal volumetric MRI change and rate of cognitive decline. *Neurology* 2005; 65:565-571.
24. Folstein MF, Folstein SE, McHugh PR. - "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. - *J Psychiatr Res* 1975 Nov;12(3):189-98.
25. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. - Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. - *Neurology* 2001 May 8;56(9):1133-42.
26. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. - Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. - *Neurology* 1984 Jul;34(7):939-44.

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27. Neary D, Snowden JS, Gustafson L et al. - Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. - *Neurology* 1998 Dec;51(6):1546-54.
28. van Straaten EC, Scheltens P, Knol DL et al. - Operational definitions for the NINDS-AIREN criteria for vascular dementia: an interobserver study. - *Stroke* 2003 Aug;34(8):1907-12
29. McKeith IG, Dickson DW, Lowe J et al. - Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. - *Neurology* 2005 Dec 27;65(12):1863-72
30. Smith SM, Zhang Y, Jenkinson M et al. - Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. - *Neuroimage* 2002 Sep;17(1):479-89.
31. Smith SM, Jenkinson M, Woolrich MW et al. - Advances in functional and structural MR image analysis and implementation as FSL. - *Neuroimage* 2004;23 Suppl 1:S208-19.
32. Hartley SW, Scher AI, Korf ESC, White LR, Launer LJ. Analysis and validation of automated skull stripping tools: A validation study based on 296 MR images from the Honolulu Asia aging study. *Neuroimage* 2006; 30:1179-1186.
33. Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. - A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. - *Arch Neurol* 2003 Jul;60(7):989-94.
34. Fox NC, Freeborough PA. - Brain atrophy progression measured from registered serial MRI: validation and application to Alzheimer's disease. - *J Magn Reson Imaging* 1997 Nov-Dec;7(6):1069-75.
35. Fox NC, Black RS, Gilman S et al. Effects of A beta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. *Neurology* 2005; 64:1563-1572.
36. Wang D, Chalk JB, Rose SE et al. - MR image-based measurement of rates of change in volumes of brain structures. Part II: application to a study of Alzheimer's disease and normal aging. - *Magn Reson Imaging* 2002 Jan;20(1):41-8.
37. Bradley KM, Bydder GM, Budge MM et al. - Serial brain MRI at 3-6 month intervals as a surrogate marker for Alzheimer's disease. - *Br J Radiol* 2002 Jun;75(894):506-13.
38. O'Brien JT, Paling S, Barber R et al. - Progressive brain atrophy on serial MRI in dementia with Lewy bodies, AD, and vascular dementia. - *Neurology* 2001 May 22;56(10):1386-8.
39. Paviour DC, Price SL, Jahanshahi M, Lees AJ, Fox NC. Longitudinal MRI in progressive supranuclear palsy and multiple system atrophy: rates and regions of atrophy. *Brain* 2006; 129:1040-1049.
40. Sormani MP, Rovaris M, Valsasina P, Wolinsky JS, Comi G, Filippi M. - Measurement error of two different techniques for brain atrophy assessment in multiple sclerosis. - *Neurology* 2004 Apr 27;62(8):1432-4.

