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## Visualizing the Shrinking Brain: Longitudinal MR Studies in the Spectrum of Cognitive Decline

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# Chapter 6

## Whole-brain atrophy rate in Alzheimer's disease: identifying fast progressors

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## Abstract

**Objective:** To assess which baseline clinical and MRI measures influence whole-brain atrophy rates, measured from serial MR imaging.

**Patients & Methods:** We recruited 65 AD patients (age mean $\pm$ sd 70 $\pm$ 8y, 58% women, MMSE 22 $\pm$ 5), scanned with an average interval of 1.7 $\pm$ 0.6 years. Whole-brain atrophy rates were used as outcome measure. Baseline normalized brain volume, hippocampal volume and whole-brain atrophy rates were measured using 3D T1-weighted imaging. The influence of age, sex, apolipoprotein E genotype (APOE), baseline Mini-Mental State Examination (MMSE), baseline hippocampal volume, and baseline normalized brain volume on whole-brain atrophy rates was assessed using linear regression.

**Results:** The mean whole-brain atrophy rate was -1.9 $\pm$ 0.9% per year. In the multivariate model, younger age ( $\beta$ (SE)=0.03(0.01);  $p=0.04$ ), absence of APOE ( $\beta$ (SE)=0.61(0.28);  $p=0.03$ ), and a low MMSE ( $\beta$ (SE)=0.11(0.03);  $p<0.001$ ) were associated with a higher whole-brain atrophy rate. Furthermore, a relatively spared hippocampus predicted faster decline for patients with a smaller baseline brain volume ( $p=0.09$ ), and with a lower MMSE ( $p=0.07$ ). Finally, a smaller brain volume was associated with a higher rate of atrophy in younger patients ( $p=0.03$ ).

**Conclusions:** Our results suggest that is possible to characterise a subgroup of AD patients, that are at risk of faster loss of brain volume. Patients with more generalized, rather than focal hippocampal atrophy, who often have an onset before the age of 65, and are APOE  $\epsilon$  4 negative, seem to be at risk of faster whole-brain atrophy rates than the more commonly seen AD patients, who are older, APOE  $\epsilon$  4 positive and have pronounced hippocampal atrophy.

## Introduction

Alzheimer's disease is characterised by progressive cognitive impairment.<sup>1</sup> However, the course of AD is variable: not all patients progress at the same rate and the factors that influence or predict progression are not well understood.<sup>2,3</sup> Most commonly, progression of the disease is measured by change in cognition over time.<sup>2-5</sup> However, clinical and neuropsychological measures may lack sensitivity to change, are subject to day-to-day variability, and are influenced by behavioral fluctuations and intercurrent illness and medication. Neuroimaging markers provide an alternative and objective assessment of progression. The use of whole-brain atrophy rates, measured from serial MR imaging, correlates well with clinical progression in untreated subjects.<sup>6-10</sup>

Rates of whole brain atrophy within AD are most typically reported to amount to 2% per year<sup>11</sup>, with substantial variability among populations studied (1% to 4%).<sup>7,12</sup> Little is known about the determinants of this variability. We wished to assess which baseline demographic, clinical, and MRI variables influence whole-brain atrophy rates in AD.

## Material and methods

### Patients

We recruited 65 patients with clinically diagnosed AD attending our memory clinic. Patients underwent a standardized clinical assessment at baseline, including medical history, physical and neurological examination, laboratory tests, psychometric evaluation, and brain MRI. The mini-mental state examination (MMSE) was used as a measure of general cognitive function.<sup>13</sup> Diagnoses were established during a multidisciplinary consensus meeting according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) criteria for probable AD.<sup>14</sup> Based on age at baseline MRI (roughly corresponding to age at diagnosis), patients were dichotomised in early onset ( $\leq 65$  years) and late onset ( $>65$  years) AD. The study was approved by the institutional ethical review board and all subjects gave written informed consent.

### APOE

DNA was isolated from 10 ml EDTA blood. Apolipoprotein E (APOE) genotype was determined with the Light Cycler APOE mutation detection method (Roche Diagnostics GmbH, Mannheim, Germany). APOE was available from 53 of 65 patients (82%) and was dichotomized according to APOE  $\epsilon 4$  status (one or more versus no  $\epsilon 4$  alleles present).

### MRI

Between 2004 and 2006 all patients were invited for a repeat MR scan, so each of the subjects had 2 MR scans. Follow-up time is defined as time between the two MRI scans (mean interval 1.7 years, standard deviation 0.6; range 11m-4y2m). MR imaging was performed on a 1.0-T Siemens Magnetom Impact Expert scanner (Siemens AG, Erlangen, Germany) and included coronal T1-weighted 3D MPRAGE volumes (magnetization prepared rapid acquisition gradient echo; single slab 168 slices; voxel size  $1 \times 1 \times 1.5$  mm; repetition time=15ms; echo time=7ms; inversion time=300ms; flip angle  $15^\circ$ ). Subjects were included only if they had two scans of adequate quality, performed on the same scanner using the same imaging protocol. Scans were reviewed by a

radiologist to exclude non-neurodegenerative pathology that could explain the cognitive impairment. NINDS-AIREN criteria<sup>15</sup> were used to exclude patients with vascular dementia (3 patients).

### **Whole-brain volume and whole-brain atrophy rates**

Normalized baseline brain volume (NBV) and percentage brain volume change (PBVC) between two time-points were determined using SIENAX and SIENA (Structural Image Evaluation, using Normalisation, of Atrophy), two fully automated techniques part of FSL (for a detailed explanation see: [www.fmrib.ox.ac.uk/analysis/research/siena/](http://www.fmrib.ox.ac.uk/analysis/research/siena/)).<sup>16,17</sup>

Whole-brain atrophy rates were measured with SIENA. Briefly, the brain was extracted using the brain extraction tool.<sup>17</sup> Compared to standard SIENAX and SIENA, the procedure to remove non-brain tissue was slightly modified, because the brain extraction tool often leaves significant amounts of non-brain tissue (e.g. skull, meninges), while also removing cortex in some areas.<sup>18</sup> To remove all non-brain tissue without losing cortex, we incorporated registration of a template mask to the individual scans. After this modified brain extraction procedure, the standard SIENA pipeline was continued. Using affine registration, the two scans were resampled in a common space to allow the change analysis. The skull was used as a scaling constraint in this step, in order to prevent the registration from introducing differences in head size between the two time points. The change analysis was then performed by applying automated tissue type segmentation, identifying edge points between brain tissue and other substances, and then estimating the perpendicular motion of the brain edge at these edge points. Finally, the average edge motion was converted to a percentage brain volume change (PBVC) between the two timepoints

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 inter individual differences in head size, a volumetric scaling factor was obtained by affine-registering the brain image to MNI152 space, using

the skull contour to determine 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.

For SIENAX (cross-sectional) a brain volume accuracy of 0.5 to 1% has been reported, whereas for SIENA (longitudinal), an error of 0.15 to 0.20% on the PBVC scale has been reported.<sup>16</sup> All individual scans, registration results, and SIENA(X) output were reviewed by a rater who was blinded to the diagnosis. Two scans were excluded from analysis, because movement artefacts in the original MRI data led to spurious results.

### **Baseline hippocampal volume**

The in-house developed software package Show Images 3.7.0 was used for manual delineation of the baseline left and right hippocampus. The hippocampus was resliced and measured according to previously published criteria.<sup>19,20</sup> Briefly, the slice on which the hippocampal formation is first visible ventral to the amygdala was the most anterior slice measured. The ventral border is formed by the white matter of the parahippocampal gyrus. The dorsal border is formed by the amygdala in the anterior slices, more posterior cerebrospinal fluid (CSF) and the choroid plexus. The slice in which the crux of the fornix is visible in its total length was the most posterior slice measured. The dentate gyrus, cornu ammonis, subiculum, fimbria and alveus were measured (referred to as hippocampus). Measurements were performed by two operators, blinded to all clinical data. Reliability was assessed by measuring 10 brains twice: the mean intra-rater variability was below 5%, and mean inter-rater variability was below 8%. Hippocampal volume was computed by summing the delineated area of the region of interest on each slice and multiplying by the slice thickness. Left and right hippocampal volumes were averaged.

**Table 1. Baseline demographics, clinical and MRI characteristics**

	Total	Early onset AD (age≤65y)	Late onset AD (age>65)
N patients	65	26	39
Sex (women / men)	38 / 27	16 / 10	22 / 17
Age, years	70 (8)	58 (3)	73 (4)
Disease duration, years	3 (2)	3 (2)	3 (2)
No. apolipoprotein E genotype ( $\epsilon$ 4- / $\epsilon$ 4+) <sup>a</sup>	13 / 40	7 / 16	5 / 23
Baseline MMSE score	22 (5)	22 (5)	22 (4)
Average hippocampal volume, mL	2.7 (0.4)	2.8 (0.4)	2.6 (0.4) *
Normalized brain volume, mL	1453 (88)	1452 (81)	1454 (94)
Follow-up time, years	1.7 (0.6)	1.7 (0.8)	1.7 (0.5)
MMSE change (points/year) <sup>b</sup>	-2.1 (2)	-2.4 (1.6)	-1.9 (2.1)
Whole-brain atrophy rate, %/year	-1.9 (0.9)	-2.2 (1.1)	-1.7 (0.8) *

Data are displayed as mean (sd), unless indicated otherwise. To test for differences between dichotomised age-groups (young:  $\leq 65$  and old:  $> 65$ ) chi-squared test and ANOVA were used where appropriate. <sup>a</sup> = available for n=53; <sup>b</sup>= available for n=60; \*  $p < 0.05$  versus early onset AD; MMSE = Mini-Mental State Examination

## Statistics

Statistical analysis was performed with SPSS 12.0. Whole-brain atrophy rates (PBVC) were annualized by dividing by the time interval in years. A more negative whole-brain atrophy rate represents a larger relative brain volume loss per year. To test for differences between dichotomised age-groups (young:  $\leq 65$  and old:  $> 65$ ) chi-squared test and t-test were used. Associations between MMSE change and whole-brain atrophy rates were assessed using bivariate correlation. We used linear regression analysis to assess the effects of age, sex, APOE, baseline MMSE, hippocampal volume and normalized brain volume (independent variables) on whole-brain atrophy rate (dependent variable). In model 1, influence for each variable was assessed separately, univariate analyses are presented. In model 2 each variable is corrected for age and sex, which are known to influence many of the predictor variables (these two variables are tested in model containing only age and sex). Model 3 is the full model,



where the influence of all variables was tested simultaneously. Subsequently, interactions between baseline predictors were assessed, by entering bivariate interaction terms into a model containing all variables, except for APOE, as APOE data were not available for all patients. Interactions with APOE were calculated separately in the full model. When assessing interactions, dichotomised age was used (young:  $\leq 65$  and old:  $> 65$ ). In general, statistical significance was set at  $p < 0.05$ . Interactions were considered significant if p-values were lower than 0.10.

## Results

Baseline demographic, clinical and MRI characteristics are presented in Table 1. AD patients in this study on average were  $70 \pm 8$  years old, 39 patients were above the age of 65 years, and 26 were 65 years or younger. Mean baseline MMSE was  $22 \pm 5$ , indicating mild to moderate AD. The mean whole-brain atrophy rate for the AD group was  $-1.9 \pm 0.9\%$  per year. Older AD patients had smaller baseline hippocampi ( $p < 0.05$ ), and a lower whole-brain atrophy rate ( $p < 0.05$ ) compared to young AD patients. Whole-brain atrophy rate correlated with annualized change in MMSE score ( $r = 0.38$ ;  $p < 0.01$ ).

The effects of baseline demographic, clinical and MRI characteristics on whole-brain atrophy rate were evaluated using linear regression analyses (Table 2). In the univariate model, age, APOE, MMSE and hippocampal volume were associated with whole-brain atrophy rate. These effects remained comparable after correction for age and sex, and showed that earlier onset AD patients had a higher whole-brain atrophy rate, with an increase in whole-brain atrophy rate of 0.3% per year for every decade AD patients were younger. Compared with APOE  $\epsilon 4$  positive patients, APOE  $\epsilon 4$  negative patients had a 0.7% per year higher whole-brain atrophy rate. For every point lower on baseline MMSE, patients subsequently lost 0.1% more brain per year. There was an inverse relation between baseline hippocampal volume and whole-brain atrophy rate, with larger hippocampal volume being associated with a higher whole-brain atrophy rate. In model 3 (full model) the effects of age, APOE and MMSE remained significant.

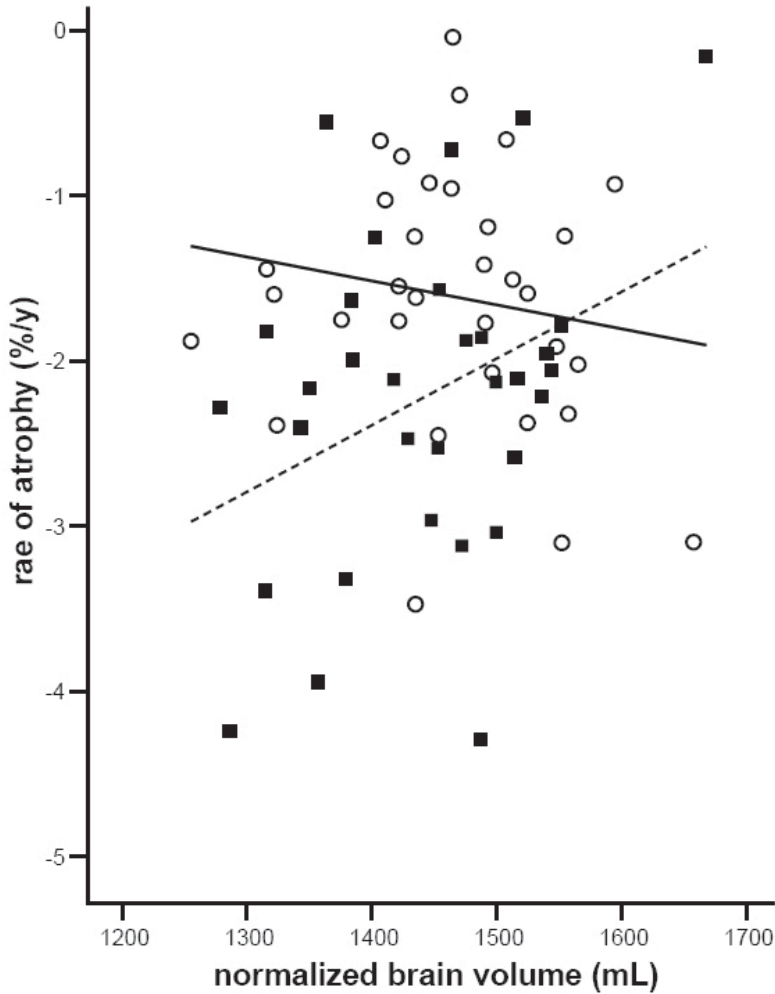
Subsequently, bivariate interaction terms were entered into the model. First, we observed an interaction between hippocampal volume and normalized brain volume ( $p=0.09$ ), indicating that in patients with a relatively spared hippocampal volume, a lower normalized brain volume was associated with a higher whole-brain atrophy rate, while this effect was not seen in patients with hippocampal atrophy at baseline (Figure 1). Secondly, there was an interaction between hippocampal volume and MMSE ( $p=0.07$ ): a lower baseline MMSE was associated with a higher whole-brain atrophy rate in patients with a relatively large hippocampal volume, while this effect was not seen in patients with a smaller hippocampal volume (Figure 2). Finally, there was an interaction between age and normalized brain volume ( $p=0.03$ ), indicating that among patients with a younger age a lower baseline normalized brain volume was associated with a higher whole-brain atrophy rate, while in patients with a higher age, normalized brain volume was not associated with whole-brain atrophy rate (Figure 3).

**Table 2. Influence of baseline demographics, clinical and MRI characteristics on whole-brain atrophy rate**

	Model 1: univariate	Model 2: age, sex	Model 3: full model
Age, per 1-year increment	0.03 (0.01) *	0.03 (0.01) *	0.03 (0.01) *
Sex, women	0.12 (0.24)	0.04 (0.23)	-0.01 (0.24)
Apolipoprotein E genotype, $\epsilon$ 4 present <sup>a</sup>	0.77 (0.30) *	0.71 (0.31) *	0.61 (0.28) *
Mini-Mental State Examination, per 1-point increment	0.09 (0.02) *	0.10 (0.02) *	0.11 (0.03) *
Hippocampal volume, per 1-mL increment	-0.60 (0.26) *	-0.46 (0.28) +	-0.03 (0.28)
Normalized brain volume, per 1-mL increment	0.002 (0.001)	0.002 (0.001) +	0.002 (0.001)

Data are presented as  $\beta$  (SE) per unit. Model 1 represents the univariate analysis. In model 2 the analysis is corrected for age and sex. Model 3 is the full model ( $n=53$ ). Negative estimates imply a higher whole-brain atrophy rate; positive estimates imply a lower whole-brain atrophy rate.

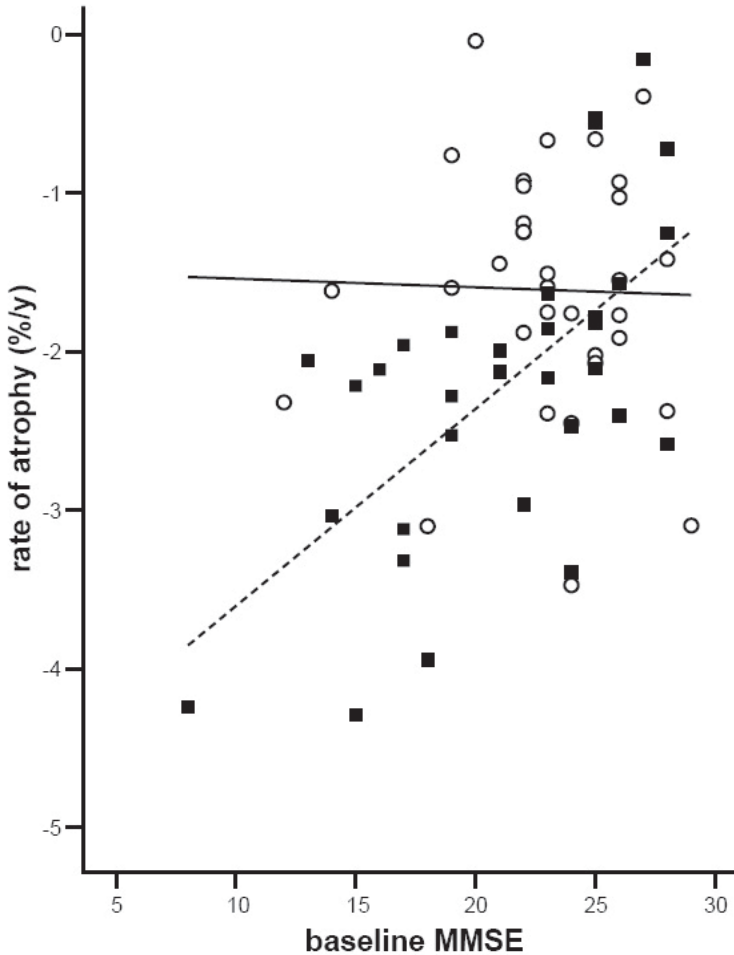
\*  $p<0.05$ ; +  $p<0.10$ ; <sup>a</sup>= available for  $n=53$



**Figure 1.** Scatter plot of whole-brain atrophy rate (%/y) by normalized brain volume (mL). For display purposes only, hippocampal volume has been dichotomized into small and large volume, based on median split. The intersecting regression lines of large (line) and small (dotted line) hippocampal volume indicate that the association between normalized brain volume and whole-brain atrophy rate is modified by the extent of hippocampal atrophy. While a low baseline brain volume is associated with a higher whole-brain atrophy rate for patients with a relatively spared hippocampus, this effect is not observed in the patient group with hippocampal atrophy.

Scatter: ○ = small hippocampus; ■ = large hippocampus

Regression line: — = small hippocampus; --- = large hippocampus

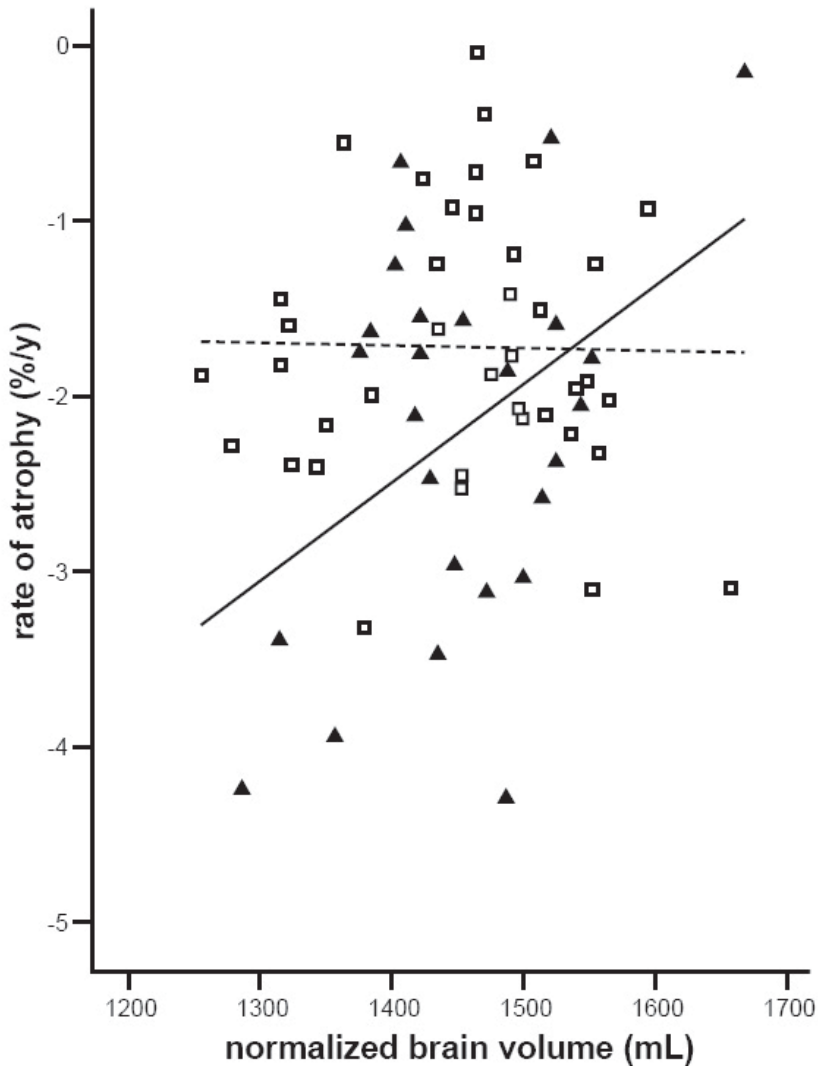


**Figure 2. Scatter plot of whole-brain atrophy rate (%/y) by baseline MMSE.**

For display purposes only, hippocampal volume has been dichotomized into large and small volume, based on median split. The intersecting regression lines of large (line) and small (dotted line) hippocampal volume indicate that whole-brain atrophy rate is differently affected by a low MMSE for patients with or without hippocampal atrophy. While a low MMSE is associated with a higher whole-brain atrophy rate for patients with a relatively spared hippocampus, this effect is not observed in patients with hippocampal atrophy.

Scatter: ▲ = small hippocampus; □ = large hippocampus

Regression line: — = small hippocampus; --- = large hippocampus



**Figure 3. Scatter plot of whole-brain atrophy rate (%/y) by normalized brain volume (mL).** Age has been dichotomized into young ( $\leq 65$  y) versus old ( $> 65$  y) Alzheimer's disease (AD) patients. The intersecting regression lines of young (line) versus old (dotted line) indicate that whole-brain atrophy rate is differently affected by the normalized brain volume in both age groups. While a low baseline brain volume for younger patients is associated with a higher whole-brain atrophy rate, indicating a faster decline, this effect is not observed in the older patient group.

Scatter: ▲ = young AD; □ = old AD

Regression line: — = young AD; --- = old AD

## Discussion

In this study we assessed which MRI and demographic factors influence whole-brain atrophy rate in a sample of patients with a clinical diagnosis of AD. The main findings are that an earlier age, absence of APOE  $\epsilon$  4 and a low MMSE at baseline were associated with higher whole-brain atrophy rate, as measured using serial MR imaging. Furthermore, a relatively spared baseline hippocampus predicted faster decline for AD patients with a smaller baseline brain volume and a lower MMSE score. Finally, a smaller brain volume was associated with a higher rate of whole brain atrophy in patients with a relatively younger age. Most studies focus on the early diagnosis of AD trying to identify diagnostic markers. Few studies have aimed at the identification of prognostic markers that influence the variation in rate of decline after patients have received the diagnosis of AD. In the majority of available studies that assess the progression of AD, change in cognitive function is used as a marker for disease progression.<sup>2-5</sup> These studies report that there is substantial heterogeneity in the progression of AD. The severity of cognitive impairment at diagnosis is suggested to be an important predictor of progression.<sup>2,3</sup> Furthermore, patients with a slow rate of cognitive decline in the early stage of AD were unlikely to show a subsequent fast progression rate.<sup>2,5</sup>

We found younger age, absent APOE  $\epsilon$  4 and low MMSE to be associated with a higher whole-brain atrophy rate. It has been suggested that the course of presenile dementia is more rapid.<sup>21</sup> Papers that address familial AD (mostly early onset) report that patients progress more rapidly compared to sporadic AD (mostly late onset).<sup>22</sup> We extend these findings by showing in a group of sporadic AD with a large variation in age, that an earlier age by itself predicts a faster whole-brain atrophy rate.

Within our sample of AD patients the presence of APOE  $\epsilon$  4 – the most important genetic risk for AD – was associated with a lower whole-brain atrophy rate. Although in the non-demented elderly population APOE  $\epsilon$  4 has shown to be associated with a higher rate of decline, this is attributable to APOE  $\epsilon$  4 being a risk factor for AD and does not necessarily imply an effect on progression in established disease.<sup>23,24</sup> The few studies that assess the effects of APOE  $\epsilon$  4 on the rate of progression within AD tend to have comparable findings with our study. One study of AD patients reported that APOE  $\epsilon$  4 carriers performed better on the MMSE.<sup>4</sup> In another paper the proportion of APOE  $\epsilon$  4 carriers

was not different between fast and slow progressing AD patients, though this was not formally tested.<sup>7</sup> This would imply that APOE  $\epsilon$  4 carriers, once they reach the AD stage, do not have atrophy rates that are more rapid than AD non-carriers.

Finally, inspection of interactions showed that a smaller brain volume was associated with a higher whole-brain atrophy rate in patients with an early age. Furthermore a relatively spared hippocampal volume was predictive of a higher whole-brain atrophy rate in AD patients with a smaller normalized brain volume and a lower MMSE. At first sight, it seems counterintuitive, that patients with a large hippocampal volume were predisposed to a higher whole-brain atrophy rate. However, this effect was specific for those patients who in addition had a small baseline brain volume or low MMSE. These results suggest that patients with early brain volume loss due to atrophy in other regions than the medial temporal lobe, are at risk of faster decline, especially when they have an earlier age. Among the strengths of this study is the number of AD patients, who were collected in one center and underwent serial MR imaging on the same scanner. Patients were characterized in a uniform manner and the relatively large diagnosis was determined by a multidisciplinary team. Limitations of the study include that, even though we included a relatively large number of AD patients, these were not pathologically proven and not more than one repeated MRI scan was obtained per patient to monitor the course of the disease. Furthermore, APOE genotyping was missing in a minority of patients. Our AD patient sample was relatively young, with a mean age of 70 years. This can be explained by the fact that patients were recruited at a tertiary referral center, where many patients with early onset dementia are evaluated. The broad age range of our patient sample provided us with the unique opportunity to explore the effect of age on clinical characteristics of AD.

Clinically, different phenotypes of AD have been described.<sup>25,26</sup> It has been suggested that AD patients with an onset before the age of 65, who are APOE  $\epsilon$  4 negative often have a distinct clinical profile, with prominent parietal dysfunction.<sup>27,28</sup> It is tempting to think that these patients have early biparietal and more generalized atrophy, rather than focal medial temporal lobe atrophy. Our data suggest that these patients may be at risk of faster global disease progression than the more commonly seen sporadic AD patients, who are older, APOE  $\epsilon$  4 positive and have pronounced hippocampal atrophy.

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