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Chapter 5

Hippocampal atrophy rates in Alzheimer disease: Added value over whole-brain volume measures

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Abstract

Objective: To investigate the added value of hippocampal atrophy rates over whole brain volume measurements on MRI in patients with AD, mild cognitive impairment (MCI) and controls.

Methods: We included 64 AD patients (67±9 yrs.; f/m 38/26), 44 MCI patients (71±6 yrs; 21/23) and 34 controls (67±9 yrs.; 16/18). Two MR-scans were performed (scan interval: 1.8±0.7 yrs., 1.0T), using a coronal 3D T1-weighted gradient echo sequence. At follow-up, three controls and 23 MCI patients had progressed to AD. Hippocampi were manually delineated at baseline. Hippocampal atrophy rates were calculated using regional, non-linear 'fluid' registration. Whole brain baseline volumes and atrophy rates were determined using automated segmentation and registration tools.

Results: All MRI measures differed between groups (p<0.005). For the distinction of MCI from controls, larger effect sizes of hippocampal measures were found compared to whole brain measures. Between MCI and AD, only whole brain atrophy rate differed significantly. Cox proportional hazards models (variables dichotomized by median) showed that within all non-demented patients, hippocampal baseline volume (hazard ratio [HR]: 5.7[95%CI:1.5-22.2]), hippocampal atrophy rate (5.2[1.9-14.3]) and whole brain atrophy rate (2.8[1.1-7.2]) independently predicted progression to AD; the combination of low hippocampal volume and high atrophy rate yielded a HR of 61.1 (6.1-606.8). Within MCI patients, only hippocampal baseline volume and atrophy rate predicted progression.

Conclusion: Hippocampal measures, especially hippocampal atrophy rate, best discriminate MCI from controls. Whole brain atrophy rate discriminates AD from MCI. Regional measures of hippocampal atrophy are the strongest predictors of progression to AD.

Introduction

Underlying clinical progression in Alzheimer's disease are neuropathological changes that follow a pattern of regional spread throughout the brain, starting at the medial temporal lobe and gradually effecting other parts of the cerebral cortex in later stages.[1] Especially with the prospect of disease-modifying therapies, early detection and monitoring of progression are important research goals in AD. Two frequently studied in *vivo* markers for diagnosis and disease progression in AD are whole brain atrophy and hippocampal atrophy on MRI. Both whole brain atrophy[2-4] and hippocampal atrophy[4] distinguish AD patients from controls and correlate with cognitive decline.[5,6] Within MCI patients, hippocampal atrophy predicts future progression to AD,[7,8] and in a recent study, we showed that whole brain atrophy rate distinguished groups and predicted progression to dementia in a cohort of AD, MCI and controls.[9] Former studies mostly focused on either hippocampal or whole brain measurements in isolation. There are few studies that directly compared the predictive value of hippocampal and whole brain measures, and they yield inconsistent results.[3,10] The discrepancy between studies may in part reflect technical difficulties in measuring change, especially for the hippocampal region, which is often determined using manual outlining. In the present study, we applied a novel, semi-automated regional registration method to measure hippocampal atrophy rate, that was shown to be superior to manual segmentation.[11] We directly compare the hippocampal atrophy rates with whole brain volume measurements and hippocampal baseline volume in the same sample.

Methods

Patients and clinical assessment

We studied a cohort of 154 subjects attending our memory clinic, with a diagnosis of probable AD, MCI as well as controls, of whom we had obtained serial MRI scans. Patients with evidence of other (concomitant) disease on MRI (n= 7), or with insufficient scan quality (n=5) were excluded. In total, 142 patients were available for the present study: 64 patients with AD, 44 patients with MCI and 34 controls; this control group consisted of 26 patients with subjective complaints and 8 healthy volunteers. The study was approved by the institutional ethical committee and all subjects or their caregivers gave written informed consent for their clinical and MRI data to be used for research purposes.

All patients underwent a standardized clinical assessment, including medical history taking, neurological examination, neuropsychological examination, and MRI. Diagnoses were made in a multidisciplinary consensus meeting. The NINCDS-ADRDA criteria[12] were used for the diagnosis of AD. MCI subjects met the Petersen criteria,[13] based on subjective and objective cognitive impairment, predominantly affecting memory, in the absence of dementia or significant functional loss, with a Clinical Dementia Rating[14] of 0.5. Visual association test (VAT)[15] was used to assess memory. Language and executive functioning were tested using the category fluency test, where patients had to produce the name of as many animals as possible within one minute. Activities of daily living were assessed by an interview, structured by the instrumental activities of daily living scale.[16] The group of controls contained patients presenting with cognitive complaints in the absence of cognitive deficits on neuropsychological examination. We additionally included volunteers without memory complaints, mostly caregivers of patients visiting our memory clinic. Because there were no differences in age, sex, baseline MMSE or scan interval between patients with subjective complaints and volunteers, these two groups were pooled into one group (controls). Baseline demographic and clinical data by diagnostic group are shown in Table 1. Patients with MCI were slightly older than patients with AD and controls. There were no differences between groups in the distribution of sex or the length of the scan interval.

Non-demented participants (MCI and controls) visited the memory clinic annually. At follow-up visit, diagnostic classification was re-evaluated according to published consensus criteria. Within the group of MCI patients,[23] patients progressed to AD during follow-up, and five patients were diagnosed with another type of dementia; two with vascular dementia (VaD)[17], two with fronto-temporal lobar degeneration (FTLD)[18] and one with dementia with Lewy bodies[19]. Of the controls, three subjects progressed to AD during follow-up and one progressed to FTLD.

MRI scan acquisition and image processing

MRI scans were acquired at 1.0Tesla (Siemens Magnetom Impact Expert System, Siemens AG, Erlangen, Germany). All patients were actively invited for a follow-up MRI scan, using the same scanner and exactly the same scan protocol. Mean ±SD scan interval was 1.8 ±0.7 years. Scan protocol included a coronal, 3D, heavily T1-weighted single slab volume sequence (magnetization-prepared, rapid acquisition gradient echo sequence [MP-RAGE]); rectangular 250mm FOV with a 256x256 matrix; 1.5mm slice thickness; 168 slices; 1x1mm in plane resolution; TR=15ms; TE=7ms;TI=300ms; flip angle 15o.

Baseline 3DT1-weighted volume scans were reformatted in 2mm slices (in plane resolution 1x1mm) perpendicular to the long axis of the left hippocampus. Hippocampi on both sides were manually delineated using the software package Show_Images 3.7.0 (in-house developed at VU University Medical Center, 2003), by three trained technicians (coefficients of variation: Inter-rater<8%, intra-rater<5%). The technicians were blinded to diagnosis. Previously described criteria were used for the segmentation of the hippocampus.[20,21] The region of interest (ROI) includes the dentate gyrus, cornu ammonis, subiculum, fimbriae and alveus. Baseline hippocampal volume was calculated by multiplying the total area of all ROIs of each hippocampus by slice thickness. Baseline hippocampal volumes were adjusted for intracranial volume, using the scaling factor derived from SIENAX (see below).

For the measurement of hippocampal atrophy rate, regional non-linear 'fluid' registration was used.[22-24] First, a global, linear brain to brain registration (six degrees of freedom [dof]) was performed using the in-house developed

registration tool 'visual register'. Subsequently, the software package MIDAS[25] was used to perform two consecutive regional registration steps. A local six dof registration was performed, to further align the hippocampal region on baseline and repeat scans. Subsequently, a cuboid extending 16 voxels in all three perpendicular directions from the extreme margins of the baseline hippocampal ROI was applied to the baseline and locally registered follow-up scan. A linear intensity drop-off was created in the outer eight voxels of this cuboid to facilitate the non-linear registration. Finally, non-linear 'fluid' registration was performed within the same region, as described previously.[11] The volume change was calculated by quantification of the Jacobian values, derived from the deformation matrix. This quantification was restricted to voxels within the baseline hippocampal region that showed contraction at follow-up.[11] Atrophy rate was expressed as percentage change from baseline volume.

Normalized brain volume (NBV) and percentage brain volume change (PBVC) over time were calculated from the 3DT1 weighted images, as previously described,[9] using SIENAX (structural image evaluation, using normalization, of atrophy, cross-sectional) and SIENA (structural image evaluation, using normalization, of atrophy), both part of FMRIB's Software Library (FSL www.fmrib.ox.ac.uk/analysis/research/siena).[26] In short, brain extraction tool (BET) was used to create brain and skull masks for the baseline and follow-up images. A scaling factor was derived from an affine (12dof) registration of the baseline brain to a reference image (MNI-152)[27], using the skull to constrain the scaling and skew. NBV was derived from a tissue-type segmentation of brain tissue, using the scaling factor to normalize the baseline brain volume. For PBVC, baseline and follow-up images were registered half-way to each other. Tissue-type segmentation was performed, and the brain surface was estimated on both scans based on the border between brain and CSF. The displacement of follow-up brain surface compared with baseline was calculated as the edge-point displacement perpendicular to the surface. Subsequently, the mean edge-point displacement was converted into a global estimate of PBVC.

Statistical analyses

Statistical analyses were performed using SPSS 15.0 for Windows. Atrophy rates were divided by scan interval to obtain annualized atrophy rates. For hippocampal measures, we used the mean of left and right values. Differences between groups for categorical variables were assessed using Chi-squared tests. Analysis of variance (ANOVA), corrected for age and sex, was used to assess differences between groups for continuous variables. Post-hoc analysis of between-group differences was performed using t-tests with Bonferroni correction. To compare sensitivity to the contrasts between controls and MCI and between MCI and AD, effect sizes were calculated using the difference of the means, divided by root of the mean square error of the difference (adapted from Cohen's d, to adjust for group differences in variance). Partial correlations, controlling for age and sex, were performed between MRI measures and baseline scores on cognitive tests. Subsequently, we estimated the risk of progression, related to the four measures, using Cox proportional hazards models. The MRI measures were dichotomized, based on their median value (hippocampal baseline volume 3652mm3, atrophy rate -3.3%/yr; whole brain baseline volume 1487ml, atrophy rate -0.3%/yr). Primary outcome was progression to AD, excluding six patients who progressed to another type of dementia. Each MRI measure was entered separately, unadjusted for covariates (model 1), adjusted for age, sex and MMSE (model 2), and together with age, sex, MMSE and the other MRI variables (model 3). We repeated the Cox-regression analysis with progression to dementia as outcome, including all patients. Finally, to explore the combined effect of baseline volume and atrophy rates within the non-demented subjects, we constructed 4 groups by median values of each variable: (1) high baseline volume and low atrophy rate, (2) high baseline volume and high atrophy rate, (3) low baseline volume and low atrophy rate and (4) low baseline volume and high atrophy rate. These were entered as categorical variables into the analysis, together with the covariates age, sex and MMSE. All Cox-regression analyses were performed within all non-demented patients and within MCI patients separately.

Results

Baseline volumes and atrophy rates for each diagnostic group are presented in Table 1. Figure 1 represents box plots of the four MRI markers per diagnostic group and atrophy rates in MCI patients that remained stable and had progressed to AD at follow-up. Adjusted for age and sex, all four MRI markers differed between groups ($p<0.005$). Post-hoc analyses with Bonferroni correction (adjusted for age and sex) showed that all four MRI markers differed between controls and patients with AD ($p<0.005$). MCI patients had lower hippocampal baseline volumes and higher hippocampal atrophy rates than controls ($p<0.005$), but hippocampal baseline volumes and atrophy rates did not distinguish AD from MCI patients.

Table 1: Population descriptors and MRI measures per diagnostic group

	Controls	MCI	AD	Total
Number of subjects (n)	34	44	64	142
Progression to AD (n)	3	23	-	26
Progression to dementia (n)	4	28	-	32
Age	67 (9)	71 (6) †	67 (9) *	68 (8)
Sex (n [%] male)	18 (53%)	23 (52%)	26 (41%)	67 (47%)
scan interval	1.9 (0.9)	1.9 (0.7)	1.7 (0.6)	1.8 (0.7)
MMSE on baseline	28 (2)	26 (3) †	22 (5) *, †	25 (4)
Visual association test	11 (1)	8 (3) †	5 (3) *,†	7 (4)
Category fluency	21 (7)	17 (5) †	13 (5) *,†	16 (6)
Hippocampus				
Baseline volume	4065 (357)	3633 (489) †	3537 (634) †	3693 (572)
Atrophy rate	-2.2 (1.4)	-3.8 (1.2) †	-4.0 (1.2) †	-3.5 (1.4)
Whole brain				
Baseline volume	1534 (93)	1480 (77)	1453 (89) †	1480 (92)
Atrophy rate	-0.6 (0.6)	-1.3 (0.9) †	-1.9 (0.9) *, †	-1.4 (1.0)

Data represent mean ±SD, unless indicated otherwise. Baseline hippocampal volume is represented in mm3, baseline brain volume in ml., hippocampal and brain atrophy rate in %/year volume change. For visual association test and category fluency, data was available for 103 subjects. MCI: mild cognitive impairment; MMSE: Mini-mental status examination
* $p<0.05$ compared with MCI
† $p<0.05$ compared with controls

The two outliers with the highest hippocampal atrophy rate in controls (Figure 1B) represent two subjects that had progressed to AD at follow-up. Baseline whole brain volume did not differ between controls and MCI, nor between patients with MCI and AD. In contrast, whole brain atrophy rates were higher in MCI than in controls (p<0.005), and were again higher in AD (p<0.005). The four outliers with highest whole brain atrophy rate within MCI (Figure 1D) had progressed to either AD (n=3) or FTLD (n=1) at follow-up. MCI patients that had progressed to AD at follow-up showed higher hippocampal atrophy rates than MCI patients that remained stable (Figure 1E), and there was no difference for whole brain atrophy rate (Figure 1F).

For the difference between controls and MCI, effect size (95% CI) of baseline hippocampal volume (0.73 [0.17-1.30]) was higher than that of baseline whole brain volume (0.49 [0.17-1.30]). Likewise, the effect size of hippocampal atrophy rate (1.17 [0.60-1.73]) was higher than that of whole brain atrophy rate (0.86 [0.30-1.43]). These results suggest a greater value of regional hippocampal measures, especially atrophy rates, in discriminating MCI from controls. In contrast, when looking at the difference between MCI and AD, effect sizes for both whole brain measures (baseline volume: 0.47 [-0.02-0.96]; atrophy rate: 0.67 [0.17-0.1.16]) were larger than for hippocampal measures (baseline volume: 0.33 [-0.16-0.82]; atrophy rate 0.25 [-0.24-0.74]), implying that whole brain measures provide more discriminatory value when comparing patients with AD and MCI.

Within the total population, we found correlations of hippocampal volume with baseline scores on VAT (r: 0.35; p<0.05), of hippocampal atrophy rate with baseline MMSE, VAT and category fluency (r: 0.25, 0.38 and 0.26; p<0.05), of baseline whole brain volume with baseline MMSE and VAT (r: 0.26 and 0.29; p<0.05) and of whole brain atrophy rate with baseline MMSE, VAT and category fluency (r: 0.41, 0.32 and 0.36; p<0.05).
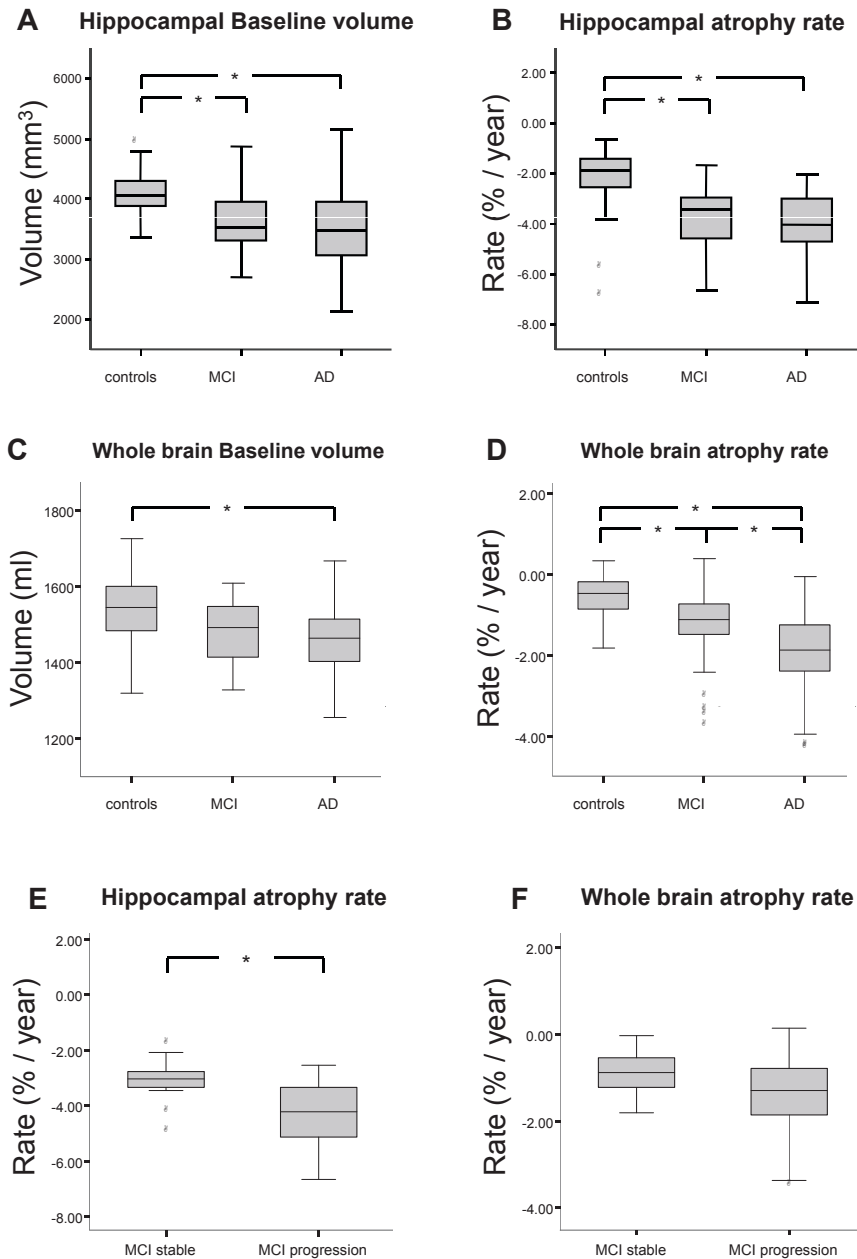
Figure 1. Mean volumes and atrophy rates. Box plots per diagnostic groups of (A) baseline hippocampal volume, (B) hippocampal atrophy rate, (C) baseline whole brain volume and (D) whole brain atrophy rate per diagnostic group (controls, MCI and AD), and box plots of MCI patients that remained stable and those who progressed to AD for (E) hippocampal atrophy rate and (F) whole brain atrophy rate. Lines represent median, boxes interquartile range and whiskers range; o: outliers * p<0.005
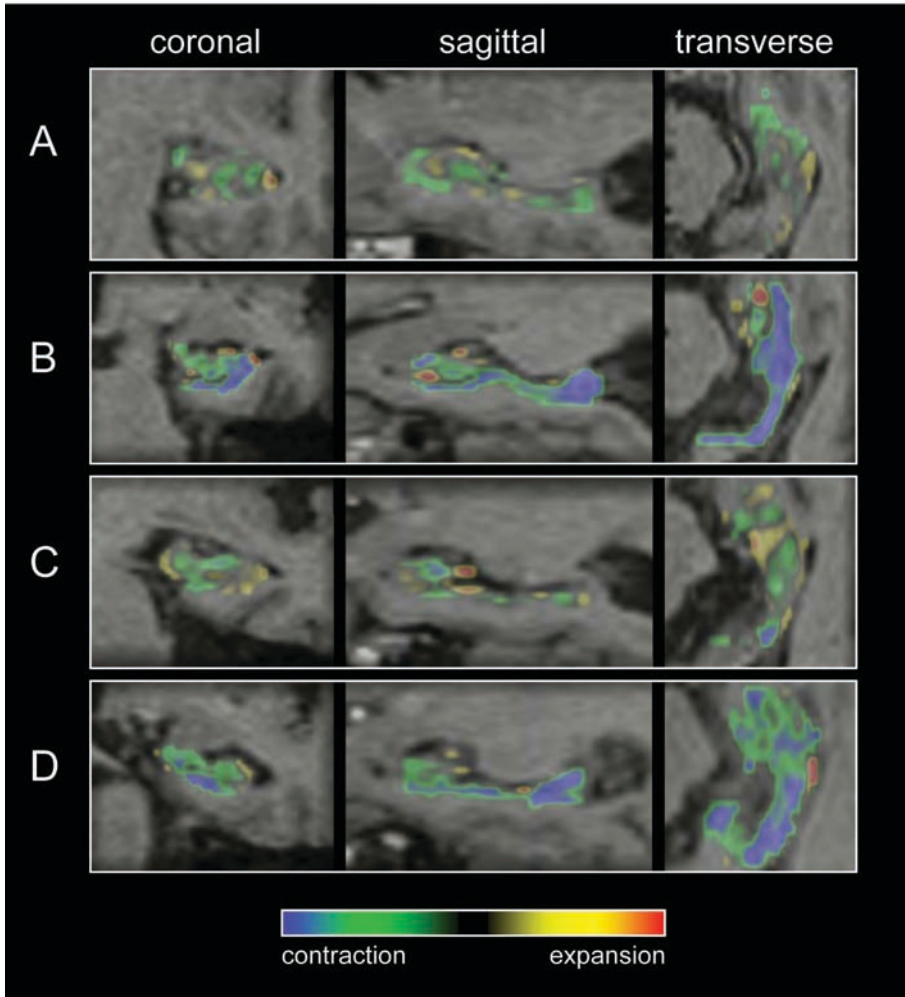
Figure 2. Individual examples of color overlay, representing contraction (green and blue) and expansion (yellow and red) within the right hippocampal ROI's of (A) a control that remained stable, (B) a control that had progressed to AD at follow-up (C) a MCI patient that remained stable and (D) a MCI patient that progressed to AD during follow-up.

A Baseline volume
B Atrophy rate

Numbers at risk

Follow-up (years):	0	1	2	3
Highest volume	36	34	19	5
Lowest volume	36	33	20	5

Numbers at risk

Follow-up (years):	0	1	2	3
Lowest atrophy rate	36	33	21	6
Highest atrophy rate	36	34	18	4

Numbers at risk

Follow-up (years):	0	1	2	3
Highest volume	36	35	22	7
Lowest volume	36	32	17	3

Numbers at risk

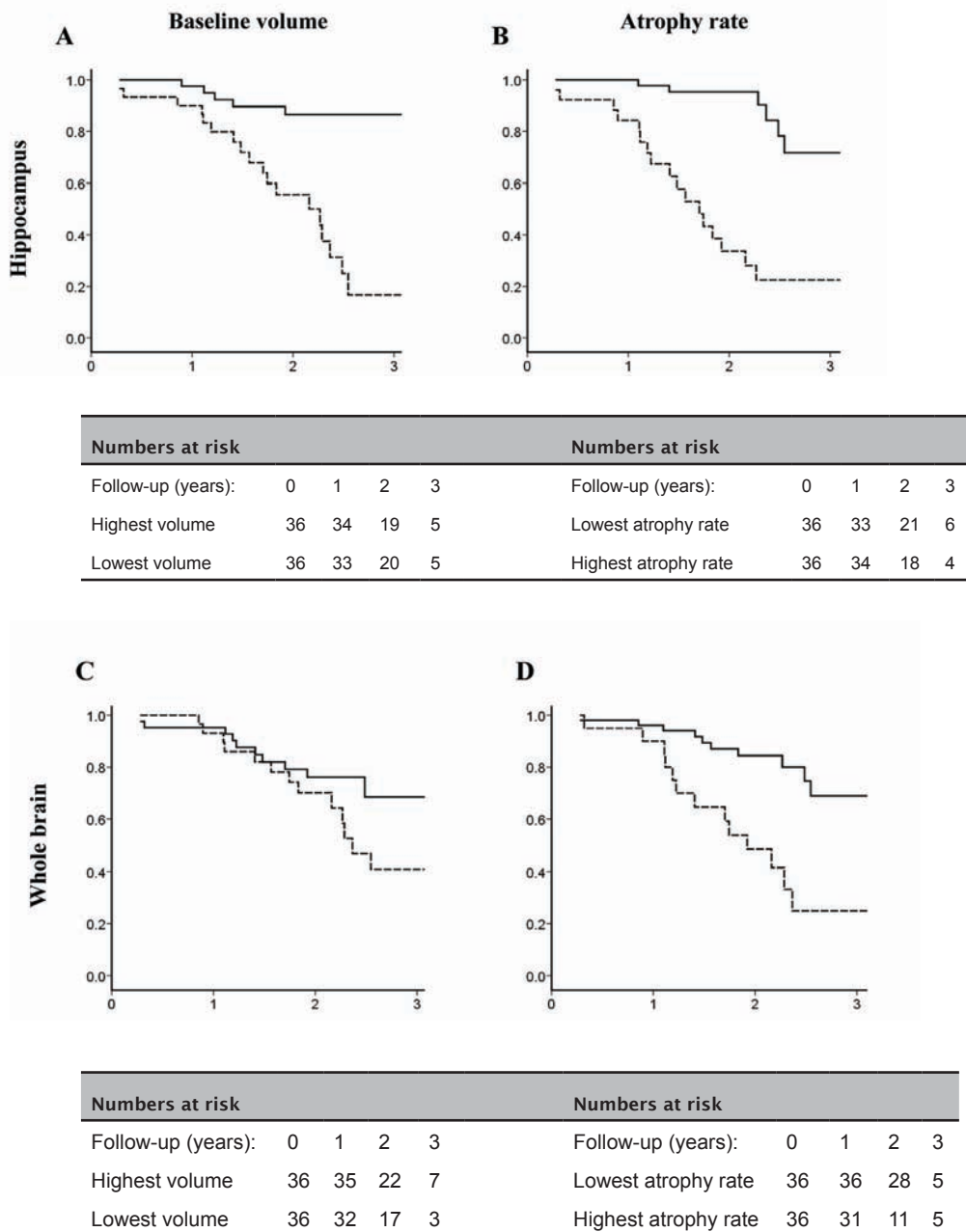| Follow-up (years):	0	1	2	3
Lowest atrophy rate	36	36	28	5
Highest atrophy rate	36	31	11	5

Figure 3. Kaplan-Meier curves of time to conversion within all non-demented subjects at baseline. MRI markers were dichotomised based on the median value: (A) baseline hippocampal volume, (B) hippocampal atrophy rate, (C) baseline whole brain volume and (D) whole brain atrophy rate. On the X-axis: follow-up duration (years); on the Y-axis: proportion of subjects that remained stable. Filled line: highest baseline volume (A; C) or lowest atrophy rate (B; D). Dotted line: lowest baseline volume (A; C) or highest atrophy rate (B; D). Tables represent the number of patients exposed to risk at the intervals of 0; 1; 2 and 3 years

Cox proportional hazard models (Table 2) show that within non-demented patients (MCI and controls), lower baseline hippocampal volume and higher hippocampal atrophy rate, as well as higher whole brain atrophy rate, independently predicted progression to AD. Baseline brain volume did not predict clinical progression. Hippocampal markers seemed to be stronger predictors than whole brain markers, with a roughly twofold higher risk. Kaplan-Meier curves for the MRI markers are shown in Figure 3. When the analysis was resctricted to MCI patients, hippocampal baseline volume had the highest predictive value. Hippocampal atrophy rate was an independent, additional predictor. However, neither whole brain volume measure predicted progression to AD. Using progression to dementia as an outcome instead of progression to AD, hippocampal baseline volume (HR [95% CI]: 2.3 [1.1-6.2]), hippocampal atrophy rate (3.8 [1.7-8.6]) and whole brain atrophy rate (2.4 [1.1-5.3]) predicted progression to dementia in model 2, and only hippocampal atrophy rate (3.0 [1.3-7.0]) was an independent predictor of progression in model 3. Within MCI patients, hippocampal baseline volume (model 2: 5.0 [2.0-12.6], model 3: 4.9 [1.8-13.2]) and hippocampal atrophy rate (model 2: 2.7 [1.2-6.3], model 3: 2.1 [0.9-5.0]) predicted progression to dementia.

Table 2: Risk of progression to AD

		Model 1	Model 2	Model 1
A. all non-demented patients (n=72)				
Hippocampus	Baseline volume	6.7 (2.5-18.1) *	5.0 (1.5-16.1) *	5.7 (1.5-22.2) *
	Atrophy rate	8.6 (3.4-21.9) *	6.2 (2.4-16.2) *	5.2 (1.9-14.3) *
Whole brain	Baseline volume	2.2 (1.0-5.0)	1.4 (0.6-3.6)	1.4 (0.5-4.2)
	Atrophy rate	3.3 (1.5-7.3) *	3.5 (1.5-8.2) *	2.8 (1.1-7.2) *
B. MCI patients (n=39)				
Hippocampus	Baseline volume	7.4 (2.4-23.0) *	10.4 (3.1-34.8) *	9.0 (2.5-32.3) *
	Atrophy rate	3.9 (1.6-9.9) *	4.5 (1.7-11.9) *	3.6 (1.2-10.7) *
Whole brain	Baseline volume	1.1 (0.5-2.5)	1.1 (0.5-2.7)	1.0 (0.4-2.5)
	Atrophy rate	1.3 (0.6-3.1)	1.2 (0.5-3.1)	1.0 (0.4-2.7)

Data represent hazard ratio (95% confidence interval) of each MRI measure for the progression to Alzheimer's disease in (A) all non-demented subjects (n=72; 26 progressed to AD) and in (B) MCI patients, (n=39; 23 progressed to AD).Model 1: unadjusted; Model 2: individual MRI measure, adjusted for age, sex and baseline MMSE; Model 3: includes all MRI measures, adjusted for age, sex and baseline MMSE.
* p<0.05

Finally, we addressed the combined effect of baseline volume and atrophy rate on the prediction of progression to AD. Within all non-demented subjects, patients with a combination of both low baseline hippocampal volume and high hippocampal atrophy rate (median split) had a far more increased risk of progression to AD (HR 61.1[95% CI: 6.1-606.8]), compared with patients with either a low baseline volume (11.2[1.1-111.1]) or a high atrophy rate (12.8[1.4-112.9]). Within MCI patients, we observed a comparable, yet less pronounced effect; HR (95%CI) 20.4 (3.9-107.2) for the combination of low hippocampal baseline volume and high atrophy rate versus 11.3 (2.0-62.8; only low baseline volume) and 5.6 (1.0-30.9; only high atrophy rate). For whole brain measures, we did not observe this increased risk for the combination of low baseline volume and high atrophy rate.

Discussion

Hippocampal baseline volume, in particular hippocampal atrophy rate, were better able to discriminate MCI patients from controls than whole brain measures. Whole brain volume measures better discriminated AD from MCI. Within non-demented subjects, regional hippocampal measures were the strongest predictors of progression to AD, but whole brain atrophy rate had an additional independent predictive effect. Within MCI patients, baseline hippocampal atrophy was the strongest predictor of progression to AD.

The atrophy rates we report are consistent with atrophy rates reported by other studies.[2, 28-30] One previous study that directly compared the sensitivity of hippocampal and whole brain atrophy rates reported that both hippocampal and whole brain measures discriminated AD from controls and cognitively impaired subjects, but neither measure distinguished controls from the cognitively impaired.[10] The apparent difference with our findings can be explained by the fact that their group of cognitively impaired did not meet MCI criteria[13], and contained no subjects that progressed to dementia at follow-up. We found stronger correlations with baseline scores on cognitive tests for whole brain measures than for hippocampal measures, which is congruent with findings by other studies.[31]

Where hippocampal measurements are more sensitive markers early in the disease, we observe a shift towards an advantage of the use of whole brain volume measurements at a later stage. Moreover, we show that both hippocampal baseline volume and atrophy rate can be used to distinguish controls from MCI and predict progression, whereas of the whole brain measurements, only atrophy rate is able to do this. This finding seems to reflect that at the stage of MCI, considerable hippocampal atrophy has already taken place. Within MCI patients, baseline hippocampal volume was an even stronger predictor than hippocamal atrophy rate, and whole brain volume did not predict progression at all in this group. We showed that combining hippocampal baseline volume and atrophy rate leads to a much higher risk on progression than when either one is present. The predictive value of whole brain and hippocampal atrophy rates was lower in MCI patients than in the group of all non-demented subjects. This implies that the predictive effects of

these longitudinal measures are strongly driven by those patients that were at a very early stage (controls) at baseline, and showed fast progression from control to AD at follow-up, with concomitant high atrophy rates.

The fact that our controls included patients with subjective cognitive complaints might be seen as a limitation of our study. Indeed, with three of the 34 controls progressing to AD, our group contained a relatively high number of patients with pre-symptomatic pathology. Although the proportion of subjects that progress to AD or dementia in our MCI and control groups are higher than reported in community-based studies,[32] they are comparable with other studies within memory clinic populations.[33] Furthermore, we think it is a strength that our groups represent a typical memory clinic population, covering the complete cognitive continuum of AD and its preceding stages.

Our findings extend on previous studies focussing on the progressive regional distribution of atrophy in AD and its preceding stages. Between MCI patients and controls, differences in atrophy (rates) have been described in medial temporal lobe structures.[4,34,35] Increased hippocampal atrophy rates have even been found in patients with familial AD before clinical symptoms occur.[34,36] In patients with AD, more widespread atrophy in other cortical areas occurs.[4,34,35] This pattern of widespread atrophy is already evident in MCI patients later progressing to AD.[37] We show that hippocampal atrophy (rate) does not differentiate AD patients from MCI, as has also been reported by others.[8] This supports earlier findings that AD-like hippocampal atrophy rate is already established in a transitional stage (MCI).[8,34] After this stage, because whole brain atrophy rates still increase with progressing disease severity,[38,39] whole brain atrophy rate becomes a better marker of disease progression than hippocampal volume measurements.

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